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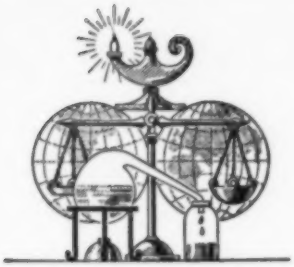

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SCIENTIFIC PROGRAMME

RECENT ADVANCES IN THERMOCHEMISTRY

I. Experimental Methods — Page

Einige neue Kalorimeter für Metallreaktionen—O. Kubaschewski (*U.K.*) 5

Zur Thermochemie von Legierungen—A. Schneider, H. Klotz, J. Stendel und G. Strauß (*Deutschland*) 13

The use of reaction calorimetric methods for measuring heats of formation of organo-metallic compounds—H. A. Skinner, J. E. Bennett and J. B. Pedley (*U.K.*) 17

A plastic capsule technique for the combustion calorimetry of volatile or chemically reactive compounds: The heat of combustion of polythene—H. Mackle and R. G. Mayrick (*U.K.*) 25

An adiabatic calorimeter for measuring heats of vaporization at 25°C—Ingemar Wadsö (*Sweden*) 29

Étude microcalorimétrique de la chaleur d'énolisation de β-dicétones—B. Jakuszewski et M. Łaźniewski (*Pologne*) 31

Fluorine bomb calorimetry—Ward N. Hubbard, Jack L. Settle and Harold M. Feder (*U.S.A.*) 39

Combustion calorimetry of organic bromine compounds: The accuracy of data obtained with a moving-bomb technique—Lars Bjellerup (*Sweden*) 45

II. Bond Energies

The heat of dissociation of nitrogen—Geo. Glockler (*U.S.A.*) 49

Heat of formation of co-ordination complexes of boron, aluminium and gallium—N. N. Greenwood and P. G. Perkins (*U.K.*) 55

Dissociation energies of metal-carbon bonds and the excitation energies of metal atoms in combination—L. H. Long (*U.K.*) 61

The thermochemistry of organo-phosphorus compounds—C. T. Mortimer (*U.K.*) 71

Thermochemistry of organic fluorine compounds and carbon compounds of metals by rotating-bomb calorimetry—W. D. Good and D. W. Scott (*U.S.A.*) 77

Thermochemie isomerer Chlortoluole—K. Schwabe, A. Schlaubitz und W. Wagner (*Deutschland*) 83

III. Specific Studies

Étude thermodynamique des réactions de double decomposition en phases solides—S. Gromb et A. Pacault (*France*) 93

Étude thermodynamique d'un halogénure mixte de cuivre—Rene Perret (*France*) 101

Equilibrium studies on disulphides using vapour phase chromatography—C. J. Olander and S. Sunner (*Sweden*) 117

Zur Thermochemie der Trithiokarbonate—G. Gattow (*Deutschland*) 121

The heats of combustion of phenol and the three cresols—J. D. Cox (*U.K.*) 125

Heats of combustion of butanal and some related compounds—Jan Tjebbes (*Sweden*) 129

Heats of combustion of five alkyl phenyl ketones—M. Colomina, C. Latorre and R. Perez-Ossorio (*Spain*) 133

Thermochemical investigations on methyl-substituted benzoic acids: I. Toluic acids—M. Colomina, R. Perez-Ossorio and M. L. Boned (*Spain*) 137

Heats of mixing—S. K. Das, M. Diaz-Peña and M. L. McGlashan (*U.K.*) 141

Untersuchungen über die Mischungswarmen in den Systemen: Essigsäure–Pyridin–n-Paraffine—M. Wóycicka (*Polen*) 147

IV. General Papers on Thermodynamics

Present status of the values of the fundamental constants for physical chemistry (*Summary*)—Frederick D. Rossini (*U.S.A.*) 155

Die thermodynamische Temperaturskala und ihre Realisierung unterhalb 90°K—H. van Dijk (*Holland*) 157

SCIENTIFIC PROGRAMME

IV. General Papers on Thermodynamics—*continued* Page

Thermodynamische Temperaturskala, ihre Realisierung zwischen 90° und 1500°K—Helmut Moser (*Deutschland*) 167

Thermodynamische Temperaturskala, ihre Realiesurung an festen Körpern für Temperaturen oberhalb 1500°K—C. P. Tingwaldt (*Deutschland*) 173

Design and use of aneroid bomb calorimeters—A. R. Meetham (*U.K.*) 179

Kalorimetrische Verfahren bei höheren Temperaturen—Franz Eberhard Wittig (*Deutschland*) 183

Discussion on documentation of thermochemical data—H. F. Stimson (*U.S.A.*), K. S. Pitzer (*U.S.A.*), H. Moser (*Deutschland*) 205

THERMODYNAMIC TRANSITIONS IN CONDENSED PHASES

I. Basic Studies

Irreversible thermodynamics—Kenneth S. Pitzer (*U.S.A.*) 207

Transitions and thermal anomalies in silver oxide—Kenneth S. Pitzer, Roger E. Gerkin, Lawrence V. Gregor and C. N. R. Rao (*U.S.A.*) 211

Some theoretical aspects of phase transitions—Joseph E. Mayer (*U.S.A.*) 215

Transition types in hydrocarbons and related substances—John P. McCullough (*U.S.A.*) 221

Molecular freedom in solid solutions of hydrocarbons: Some observations on possible causes of self-diffusion—J. G. Aston (*U.S.A.*) 231

Ordering transitions in symmetrical molecules—Edgar F. Westrum, Jr (*U.S.A.*) 241

Pre-freezing and pre-melting—A. R. Ubbelohde (*U.K.*) 251

The melting mechanism of the alkali thiocyanates—Elizabeth Rhodes (*U.K.*) 257

Nucleation studies on ionic melts—E. R. Buckle and A. R. Ubbelohde (*U.K.*) 263

Ionic and molecular rotation in ammonium salts and clathrate compounds—L. A. K. Staveley and N. G. Parsonage (*U.K.*) 271

Thermodynamic properties of polar substances: Enthalpy of hydrocarbon-alcohol systems—T. S. Storvick and J. M. Smith (*U.S.A.*) 275

II. Specific Studies (Transition Phenomena)

Transformations in the Ta–H and Ta–D systems—W. E. Wallace, Per Kofstad and L. J. Hyvönen (*U.S.A.*) 281

Magnetic transitions at low temperatures—J. W. Stout (*U.S.A.*) 287

Die Kristallumwandlung des Kobalts—G.-M. Schwab und W. Ludwig (*Deutschland*) 297

Solid transitions in mixed crystals of ethylene dichloride and ethylene dibromide—J. E. Spice, G. A. Harrow, C. R. McGowan and E. B. Smith (*U.K.*) 303

Thermodynamic properties of indane and indene—D. R. Stull, G. C. Sinke, R. A. McDonald, W. E. Hatton and D. L. Hildebrand (*U.S.A.*) 315

Ortho-para and isotope separations by preferential adsorption at low temperatures (*Summary*)—David White, W. J. Haubach and E. N. Lassettre (*U.S.A.*) 323

Condensed solutions of the rare gases—R. Heastie (*U.K.*) 325

Lower critical solution points in hydrocarbon mixtures—J. S. Rowlinson and P. I. Freeman (*U.K.*) 329

Recent redeterminations of the phase diagram of the system: triethylamine + water—J. F. Counsell, D. H. Everett and R. J. Munn (*U.K.*) 335

SPECIAL LECTURES

INTRODUCTION

Opening Ceremony — Page

Impact of studies of natural products on chemical industry—A. Stoll (*Switzerland*) 349

Presidential Address

Natural product chemistry—retrospect and prospect—A. Todd (*U.K.*) 359

Special Lecture

Australian natural product research—J. R. Price (*Australia*) 367

THE CHEMISTRY OF NATURAL PRODUCTS

Heterocyclic Chemistry

The total synthesis of chlorophyll—R. B. Woodward (*U.S.A.*) 383

Chemistry of the actinomycins—H. Brockmann (*German Federal Republic*) 405

Recent investigations on some alkaloids from Indian plants—T. R. Govindachari (*India*) 425

Physical Methods

Physicochemical methods of investigating natural products—H. W. Thompson (*U.K.*) 439

Application of optical rotatory dispersion studies to problems in natural products chemistry—C. Djerassi (*U.S.A.*) 475

The direct determination of the molecular structure of natural products—A. McL. Mathieson (*Australia*) 505

Aliphatic and Homocyclic Chemistry

Terpenic compounds with medium-sized rings—F. Sorm (*Czechoslovakia*) 533

Some aspects of terpenoid and steroid chemistry—D. H. R. Barton (*U.K.*) 551

Structural patterns of polyacetylenic compounds isolated from the plant family Compositae—N. A. Sorensen (*Norway*) 569

Biological Chemistry

Chemistry and biochemistry of biologically active bacterial lipids—E. Lederer (*France*) 587

The biosynthesis of polyisoprenoids—J. W. Cornforth (*U.K.*) 607

CONCLUSION

Closing Ceremony

Summary of scientific achievements of the Symposium—R. Robinson (*U.K.*) 631

AUTHOR INDEX FOR VOLUME 2

ASTON, J. G.: Molecular freedom in solid solutions of hydrocarbons: some observations on possible causes of self-diffusion, 231

BARTON, D. H. R.: Some aspects of terpenoid and steroid chemistry, 551

BENNETT, J. E.: *See* SKINNER, H. A., BENNETT, J. E. and PEDLEY, J. B.

BJELLERUP, L.: Combustion calorimetry of organic bromine compounds: the accuracy of data obtained with a moving-bomb technique, 45

BONED, M. L.: *See* COLOMINA, M., PEREZ-OSSORIO, R. and BONED, M. L.

BROCKMANN, H.: Chemistry of the actinomycins, 405

BUCKLE, E. R. and UBBELOHDE, A. R.: Nucleation studies on ionic melts, 263

COLOMINA, M., LATORRE, C. and PEREZ-OSSORIO, R.: Heats of combustion of five alkyl phenyl ketones, 133

COLOMINA, M., PEREZ-OSSORIO, R. and BONED, M. L.: Thermochemical investigations on methyl-substituted benzoic acids: I. toluic acids, 137

CORNFORTH, J. W.: The biosynthesis of polyisoprenoids, 607

COUNSELL, J. F., EVERETT, D. H. and MUNN, R. J.: Recent redeterminations of the phase diagram of the system: triethylamine + water, 335

COX, J. D.: The heats of combustion of phenol and the three cresols, 125

DAS, S. K., DIAZ-PEÑA, M. and MCGLASHAN, M. L.: Heats of mixing, 141

DIAZ-PEÑA, M.: *See* DAS, S. K., DIAZ-PEÑA, M. and MCGLASHAN, M. L.

DJERASSI, C.: Application of optical rotatory dispersion studies to problems in natural products chemistry, 475

EVERETT, D. H.: *See* COUNSELL, J. F., EVERETT, D. H. and MUNN, R. J.

FEDER, H. M.: *See* HUBBARD, W. N., SETTLE, J. L. and FEDER, H. M.

FREEMAN, P. I.: *See* ROWLINSON, J. S. and FREEMAN, P. I.

GATTOW, G.: Zur Thermochemie der Trithiokarbonate, 121

GERKIN, R. E.: *See* PITZER, K. S., GERKIN, R. E., GREGOR, L. V. and RAO, C. N. R.

GLOCKLER, G.: The heat of dissociation of nitrogen, 49

GOOD, W. D. and SCOTT, D. W.: Thermochemistry of organic fluorine compounds and carbon compounds of metals by rotating bomb calorimetry, 77

GOVINDACHARI, T. R.: Recent investigations on some alkaloids from Indian plants, 425

GREENWOOD, N. N. and PERKINS, P. G.: Heat of formation of co-ordination complexes of boron, aluminium and gallium, 55

GREGOR, L. V.: *See* PITZER, K. S., GERKIN, R. E., GREGOR, L. V. and RAO, C. N. R.

GROMB, S. et PACAULT, A.: Étude thermodynamique des réactions de double décomposition en phases solides, 93

HARROW, G. A.: *See* SPICE, J. E., HARROW, G. A., MCGOWAN, C. R. and SMITH, E. B.

HATTON, W. E.: *See* STULL, D. R., SINKE, G. C., MCDONALD, R. A., HATTON, W. E. and HILDEBRAND, D. L.

HAUBACH, W. J.: *See* WHITE, D., HAUBACH, W. J. and LASSETTRE, E. N.

HEASTIE, R.: Condensed solutions of the rare gases, 325

HILDEBRAND, D. L.: *See* STULL, D. R., SINKE, G. C., MCDONALD, R. A., HATTON, W. E. and HILDEBRAND, D. L.

HUBBARD, W. N., SETTLE, J. L. and FEDER, H. M.: Fluorine bomb calorimetry, 39

HYVÖNEN, L. J.: *See* WALLACE, W. E., KOFSTAD, P. and HYVÖNEN, L. J.

JAKUBZEWSKI, B. et LAŹNIEWSKI, M.: Étude microcalorimétrique de la chaleur d'énolisation de β-dicétones, 31

KLOTZ, H.: *See* SCHNEIDER, A., KLOTZ, H., STENDEL, J. und STRAUß, G.

KOFSTAD, P.: *See* WALLACE, W. E., KOFSTAD, P. and HYVÖNEN, L. J.

KUBASCHEWSKI, O.: Einige neue Kalorimeter für Metallreaktionen, 5

LASSETTRE, E. N.: *See* WHITE, D., HAUBACH, W. J. and LASSETTRE, E. N.

LATORRE, C.: *See* COLOMINA, M., LATORRE, C. and PEREZ-OSSORIO, R.

AUTHOR INDEX

Laźniewski, M.: *See* Jakuszewski, B. et Laźniewski, M.

Lederer, E.: Chemistry and biochemistry of biologically active bacterial lipids, 587

Long, L. H.: Dissociation energies of metal–carbon bonds and the excitation energies of metal atoms in combination, 61

Ludwig, W.: *See* Schwab, G.-M. und Ludwig, W.

Mackle, H. and Mayrick, R. G.: A plastic capsule technique for the combustion calorimetry of volatile or chemically reactive compounds: the heat of combustion of polythene, 25

Mathieson, A. McL.: The direct determination of the molecular structure of natural products, 505

Mayer, J. E.: Some theoretical aspects of phase transitions, 215

Mayrick, R. G.: *See* Mackle, H. and Mayrick, R. G.

McCullough, J. P.: Transition types in hydrocarbons and related substances, 221

McDonald, R. A.: *See* Stull, D. R., Sinke, G. C., McDonald, R. A., Hatton, W. E. and Hildebrand, D. L.

McGlashan, M. L.: *See* Das, S. K., Diaz-Peña, M. and McGlashan, M. L.

McGowan, C. R.: *See* Spice, J. E., Harrow, G. A., McGowan, C. R. and Smith, E. B.

Meetham, A. R.: Design and use of aneroid bomb calorimeters, 179

Mortimer, C. T.: The thermochemistry of organo-phosphorus compounds, 71

Moser, H.: Thermodynamische Temperaturskala, ihre Realisierung zwischen 90° und 1500°K, 167

— *See* Stimson, H. F., Pitzer, K. S. and Moser, H.

Munn, R. J.: *See* Counsell, J. F., Everett, D. H. and Munn, R. J.

Olander, C. J. and Sunner, S.: Equilibrium studies on disulphides using vapour phase chromatography, 117

Pacault, A.: *See* Gromb, S. et Pacault, A.

Parsonage, N. G.: *See* Staveley, L. A. K. and Parsonage, N. G.

Pedley, J. B.: *See* Skinner, H. A., Bennett, J. E. and Pedley, J. B.

Perez-Ossorio, R.: *See* Colomina, M., Latorre, C. and Perez-Ossorio, R.

— *See* Colomina, M., Perez-Ossorio, R. and Boned, M. L.

Perkins, P. G.: *See* Greenwood, N. N. and Perkins, P. G.

Perret, R.: Étude thermodynamique d'un halogénure mixte de cuivre, 101

Pitzer, K. S.: Irreversible thermodynamics, 207

— Gerkin, R. E., Gregor, L. V. and Rao, C. N. R.: Transitions and thermal anomalies in silver oxide, 211

— *See* Stimson, H. F., Pitzer, K. S. and Moser, H.

Price, J. R.: Australian natural product research, 367

Rao, C. N. R.: *See* Pitzer, K. S., Gerkin, R. E., Gregor, L. V. and Rao, C. N. R.

Rhodes, E.: The melting mechanism of the alkali thiocyanates, 257

Robinson, R.: Summary of scientific achievements of the Symposium, 631

Rossini, F. D.: Present status of the values of the fundamental constants for physical chemistry, 155

Rowlinson, J. S. and Freeman, P. I.: Lower critical solution points in hydrocarbon mixtures, 329

Schlaubitz, A.: *See* Schwabe, K., Schlaubitz, A. und Wagner, W.

Schneider, A., Klotz, H., Stendel, J. und Strauß, G.: Zur thermochemie von Legierungen, 13

Schwab, G.-M. und Ludwig, W.: Die Kristallumwandlung des Kobalts, 297

Schwabe, K., Schlaubitz, A. und Wagner, W.: Thermochemie Isomerer Chlortoluole, 83

Scott, D. W.: *See* Good, W. D. and Scott, D. W.

Settle, J. L.: *See* Hubbard, W. N., Settle, J. L. and Feder, H. M.

Sinke, G. C.: *See* Stull, D. R., Sinke, G. C., McDonald, R. A., Hatton, W. E. and Hildebrand, D. L.

Skinner, H. A., Bennett, J. E. and Pedley, J. B.: The use of reaction calorimetric methods for measuring heats of formation of organo-metallic compounds, 17

Smith, E. B.: *See* Spice, J. E., Harrow, G. A., McGowan, C. R. and Smith, E. B.

Smith, J. M.: *See* Storvick, T. S. and Smith, J. M.

Sørensen, N. A.: Structural patterns of polyacetylenic compounds isolated from the plant family Compositae, 569

Šorm, F.: Terpenic compounds with medium-sized rings, 533

Spice, J. E., Harrow, G. A., McGowan, C. R. and Smith, E. B.: Solid transitions in mixed crystals of ethylene dichloride and ethylene dibromide, 303

Staveley, L. A. K. and Parsonage, N. G.: Ionic and molecular rotation in ammonium salts and clathrate compounds, 271

STENDEL, J.: *See* SCHNEIDER, A., KLOTZ, H., STENDEL, J. und STRAUSS, G.

STIMSON, H. F., PITZER, K. S. and MOSER, H.: Discussion on documentation of thermochemical data, 205

STOLL, A.: Impact of studies of natural products on chemical industry, 349

STORVICK, T. S. and SMITH, J. M.: Thermodynamic properties of polar substances: enthalpy of hydrocarbon–alcohol systems, 275

STOUT, J. W.: Magnetic transitions at low temperatures, 287

STRAUSS, G.: *See* SCHNEIDER, A., KLOTZ, H., STENDEL, J. und STRAUSS, G.

STULL, D. R., SINKE, G. C., MCDONALD, R. A., HATTON, W. E. and HILDEBRAND, D. L.: Thermodynamic properties of indane and indene, 315

SUNNER, S.: *See* OLANDER, C. J. and SUNNER, S.

THOMPSON, H. W: Physicochemical methods of investigating natural products, 439

TINGWALDT, C. P.: Thermodynamische Temperaturskala, ihre Realisierung an festen Körpern für Temperaturen oberhalb 1500°K, 173

TJEBBES, J.: Heats of combustion of butanal and some related compounds, 129

TODD, A.: Natural product chemistry—retrospect and prospect, 359

UBBELOHDE, A. R.: Pre-freezing and premelting, 251

— *See* BUCKLE, E. R. and UBBELOHDE, A. R.

VAN DIJK, H.: Die thermodynamische Temperaturskala und ihre Realisierung unterhalb 90°K, 157

WADSÖ, I.: An adiabatic calorimeter for measuring heats of vaporization at 25°C, 29

WAGNER, W.: *See* SCHWABE, K., SCHLAUBITZ, A. und WAGNER, W.

WALLACE, W. E., KOFSTAD, P. and HYVÖNEN, L. J.: Transformations in the Ta–H and Ta–D systems, 281

WESTRUM, E. F.: Ordering transitions in symmetrical molecules, 241

WHITE, D., HAUBACH, W. J. and LASSETTRE, E. N.: Ortho–para and isotope separations by preferential adsorption at low temperatures, 323

WITTIG, F. E.: Kalorimetrische Verfahren bei höheren Temperaturen, 183

WOODWARD, R. B.: The total synthesis of chlorophyll, 383

WOYCICKA, M.: Untersuchungen über die Mischungswarmen in den Systemen: Essigsäure–Pyridin–n-Paraffine, 147

SUBJECT INDEX FOR VOLUME 2

Actinomycins, chemistry of, 405
Adiabatic calorimeter for measuring heats of vaporization at 25°C, 29
Adsorption at low temperatures, preferential, ortho–para and isotope separations by, 315
Alkali thiocyanates, melting mechanism of, 257
Alkaloids from Indian plants, recent investigations on some, 425
Alkyl phenyl ketones, five, heats of combustion of, 133
Aneroid bomb calorimeters, design and use of, 179
Application of optical rotatory dispersion studies to problems in natural products chemistry, 475
Australian natural product research, 367

Bacterial lipids, biologically active, chemistry and biochemistry of, 587
Biosynthesis of polyisoprenoids, 607
Butanal and some related compounds, heats of combustion of, 129

Carbon compounds of metals and organic fluorine compounds by rotating-bomb calorimetry, thermochemistry of, 77
Chaleur d'énolisation de β-dicétones, étude microcalorimétrique, 31
Chemical industry, impact of studies of natural products on, 349
Chemistry and biochemistry of biologically active bacterial lipids, 587
— of the actinomycins, 405
Chlorophyll, total synthesis of, 383
Chlortoluole, Thermochemie Isomerer, 83
Combustion calorimetry of organic bromine compounds: the accuracy of data obtained with a moving-bomb technique, 45
— — of volatile or chemically reactive compounds: the heat of combustion of polythene, plastic capsule technique for, 25
Compositae, structural patterns of polyacetylenic compounds isolated from the plant family, 569
Condensed solutions of the rare gases, 325
Constants, fundamental for physical chemistry, present status of the values of, 155
Co-ordination complexes of boron, aluminium and gallium, heat of formation of, 55

Design and use of aneroid bomb calorimeters, 179

β-Dicétones, étude microcalorimétrique de la chaleur d'énolisation, 31
Direct determination of the molecular structure of natural products, 505
Discussion on documentation of thermochemical data, 205
Dissociation energies of metal–carbon bonds and the excitation energies of metal atoms in combination, 61
Disulphides, equilibrium studies on, using vapour phase chromatography, 117
Double decomposition en phases solides, étude thermodynamique des réactions de, 93

Einige neue Kalorimeter für Metallreaktionen, 5
Enthalpy of hydrocarbon–alcohol systems, 275
Equilibrium studies on disulphides using vapour phase chromatography, 117
Essigsäure–Pyridine–n-Paraffine, Untersuchungen über die Mischungswarmen in den Systemen, 147
Ethylene dichloride and ethylene dibromide, solid transitions in mixed crystals of, 303
Étude microcalorimétrique de la chaleur d'énolisation de β-dicétones, 31
— thermodynamique des réactions de double decomposition en phases solides, 93
— — d'un halogénure mixte de cuivre, 101
Excitation energies of metal atoms in combination, and dissociation energies of metal–carbon bonds, 6

Fluorine bomb calorimetry, 39

Halogénure mixte de cuivre, étude thermodynamique de, 101
Heat of combustion of polythene, 25
— of dissociation of nitrogen, 49
— of formation of co-ordination complexes of boron, aluminium and gallium, 55
Heats of combustion of butanal and some related compounds, 129
— — of five alkyl phenyl ketones, 133
— — of phenol and the three cresols, 125
— of formation of organo-metallic compounds, reaction calorimetric methods for measuring, 17
— of mixing, 141

Heats of vaporization at 25°C, adiabatic calorimeter for measuring, 29
Hydrocarbon mixtures, low critical solution points in, 329
Hydrocarbons and related substances, transition types in, 221

Impact of studies of natural products on chemical industry, 349
Indane and indene, thermodynamic properties of, 303
Indian plants, recent investigations on some alkaloids from, 425
Ionic and molecular rotation in ammonium salts and clathrate compounds, 271
— melts, nucleation studies on, 263
Irreversible thermodynamics, 207

Kalorimeter, einige neue, für Metallreaktion, 5
Kalorimetrische Verfahren bei höheren Temperaturen, 183
Kristallumwandlung des Kobalts, 297

Legierungen, zur Thermochemie von, 13
Lipids, biologically active bacterial, chemistry and biochemistry of, 587
Lower critical solution points in hydrocarbon mixtures, 329

Magnetic transitions at low temperatures, 287
Melting mechanism of the alkali thiocyanates, 257
Metal–carbon bonds, dissociation energies of, and the excitation energies of metal atoms in combustion, 61
Metallreaktion, einige neue Kalorimeter für, 5
Methyl-substituted benzoic acids: I. toluic acids, thermochemical investigations on, 137
Mischungswarmen in den Systemen: Essigsäure–Pyridine–n-Paraffine, Untersuchungen über, 147
Mixing, heats of, 141
Molecular freedom in solid solutions of hydrocarbons: some observations on possible causes of self-diffusion, 231
Moving-bomb technique, the accuracy of data obtained with: combustion calorimetry of organic bromine compounds, 45

Natural product chemistry—retrospect and prospect, 359
— — research, Australian, 367
Natural products chemistry, application of optical rotatory dispersion studies to problems in, 475
— — impact of studies of, on chemical industry, 349
— — physicochemical methods of investigating, 439
— — the direct determination of the molecular structure of, 505
Nitrogen, heat of dissociation of, 49
Nucleation studies on ionic melts, 263

Optical rotatory dispersion studies to problems in natural products chemistry, application of, 475
Ordering transitions in symmetrical molecules, 241
Organic bromine compounds, combustion calorimetry of, the accuracy of data obtained with a moving-bomb technique, 45
— fluorine compounds and carbon compounds of metals by rotating-bomb calorimetry, thermochemistry of, 77
Organo-metallic compounds, reaction calorimetric methods for measuring heats of formation of, 17
Organo-phosphorus compounds, thermochemistry of, 71
Ortho–para and isotope separations by preferential adsorption at low temperatures, 315

Phase diagram of the system: triethylamine + water, recent determinations of, 335
— transitions, some theoretical aspects of, 215
Phases solides, étude thermodynamique des réactions de double decomposition en, 93
Phenol and the three cresols, heats of combustion of, 125
Physicochemical methods of investigating natural products, 439
Plastic capsule technique for the combustion calorimetry of volatile or chemically reactive compounds: the heat of combustion of polythene, 25
Polar substances, thermodynamic properties of: enthalpy of hydrocarbon–alcohol systems, 275
Polyacetylenic compounds isolated from the plant family Compositae, structural patterns of, 569
Polyisoprenoids, biosynthesis of, 607
Pre-freezing and pre-melting, 251
Present status of the values of fundamental constants for physical chemistry, 155

Rare gases, condensed solutions of, 325
Reaction calorimetric methods for measuring heats of formation of organo-metallic compounds, 17

Recent redeterminations of the phase diagram of the system: triethylamine + water, 335
— investigations on some alkaloids from Indian plants, 425
Rotating-bomb calorimetry, thermochemistry of organic fluorine compounds of metals by, 77
Rotation, ionic and molecular, in ammonium salts and clathrate compounds, 271

Self-diffusion, molecular freedom in solid solutions of hydrocarbons: some observations on possible causes of, 231
Silver oxide, transitions and thermal anomalies in, 211
Solid transitions in mixed crystals of ethylene dichloride and ethylene dibromide, 303
Solution points, lower critical, in hydrocarbon mixtures, 329
Some aspects of terpenoid and steroid chemistry, 551
Structural patterns of polyacetylenic compounds isolated from the plant family Compositae, 569
Summary of scientific achievements of the Symposium (on Natural Products), 631
Symmetrical molecules, ordering transitions in, 241

Terpenic compounds with medium-sized rings, 533
Terpenoid and steroid chemistry, some aspects of, 551
Theoretical aspects of phase transitions, 215
Thermochemical data, discussion on documentation of, 205
— investigations on methyl-substituted benzoic acids: I. toluic acids, 137
Thermochemie der Trithiokarbonate, 121
— Isomeres Chlortoluole, 83
— von Legierungen, 13
Thermochemistry of organic fluorine compounds and carbon compounds of metals by rotating-bomb calorimetry, 77
— of organo-phosphorus compounds, 71
Thermodynamic properties of indane and indene, 303
— — of polar substances: enthalpy of hydrocarbon–alcohol systems, 275
Thermodynamics, irreversible, 207
Thermodynamische Temperaturskala, ihre Realisierung an festen Körpern für Temperaturen oberhalb 150°K, 173
— — — zwischen 90° and 1500°K, 167
— — — unterhalb 90°K, 157
Toluic acids, thermochemical investigations on, 137
Total synthesis of chlorophyll, 383
Transformations in the Ta–H and Ta–D systems, 281
Transition types in hydrocarbons and related substances, 221
Transitions and thermal anomalies in silver oxide, 211
Triethylamine + water: recent determinations of the phase diagram of the system, 335
Trithiokarbonate, Thermochemie der, 121

Untersuchungen über die Mischungswarmen in den Systemen: Essigsäure–Pyridin–n-Paraffine, 147

Vapour phase chromatography, use of, in equilibrium studies on disulphides, 117

VOL
2
1961

EINIGE NEUE CALORIMETER FÜR METALLREAKTIONEN

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Das Schwergewicht der experimentellen Thermochemie liegt noch immer bei der Verbrennungsbombe und der Lösungscalorimetrie in wässrigen Lösungsmitteln. So nützlich diese Universalapparate sein mögen, verlieren sie doch viel an Bedeutung für die Aufklärung thermochemischer Daten der Legierungsbildung und metallurgischer Reaktionen, weil entweder die Verbrennungs- und Lösungsvorgänge der betreffenden Substanzen zu unübersichtlich sind oder die zu messenden Reaktionen zu geringe Wärmeeffekte produzieren. Im letzteren Falle erhält man das Resultat als kleine Differenz hoher Verbrennungs- oder Lösungswärmen, und die unvermeidlichen Messfehler führen zu grossen Unsicherheiten in den Endwerten. Die systematischen Messungen der Lösungwärmen von Legierungen von W. Biltz waren zweifellos eine Pionierarbeit, die Resultate jedoch noch recht unzuverlässig. Die Verbrennungscalorimetrie ist zum Studium der Bildungswärmen von Legierungen noch ungeeigneter, besonders offenbar wegen der zwar geringen aber unvermeidbaren und nicht völlig reproduzierbaren Mengen an gelöstem Wasserstoff.

Der für die genannten Reaktionen grundsätzlich geeignetere Weg ist die Direktcalorimetrie. Diese verlangt bei der oft geringen Affinität der betreffenden Substanzen die Entwicklung von Hochtemperaturcalorimetern, deren Bedeutung in Zukunft erheblich zunehmen wird. Temperatur und Arbeitsmethode sind dabei so zu wählen, dass die untersuchte Reaktion innerhalb einer experimentell vertretbaren Zeit vollständig abläuft. Relativ einfach lässt sich dies bei der Bestimmung der Mischungswärmen flüssiger Legierungen erreichen. Geeignete Calorimeter, die eine Messgenauigkeit von ± 1 Prozent erreichen, wurden z.B. von Wittig[1] und Kleppa[2] zur Untersuchung niedrigschmelzender Legierungen konstruiert. Besonders populär sind Lösungscalorimeter verschiedener Ausführung[3], die flüssiges Zinn als Lösungsmittel enthalten. Diese werden zwar meist als Differenzverfahren angewendet; da aber die Lösungswärmen in Zinn von der gleichen Grössenordnung sind wie die gesuchten Endwerte, entfallen die oben gegen die Differenzverfahren erhobenen Bedenken. Wenn die Anwendbarkeit der Zinn-Calorimeter nicht auf ein paar Legierungssysteme beschränkt bleiben soll, muss allerdings die Arbeitstemperatur beträchtlich erhöht werden, wie dies kürzlich in einem Apparat von Oriani versucht wurde[4].

Schwieriger ist die Direktcalorimetrie fester Legierungen und anderer metallurgisch wichtiger Substanzen. Wir beschäftigen uns am National Physical Laboratory seit einiger Zeit mit der Entwicklung derartiger Verfahren und wollen im folgenden kurz über die bisherigen Fortschritte berichten.

Einen einfachen Versuch, zu entscheiden, ob sich Eisen und Chrom schwach exotherm oder endotherm legieren, hat Mr W. A. Dench angestellt: s. *Abb. 1.* Zwei Zylinder (Durchmesser 15 mm) mit je einer axialen Bohrung, der eine aus reinem Nickel, der andere ein Pressling aus einer

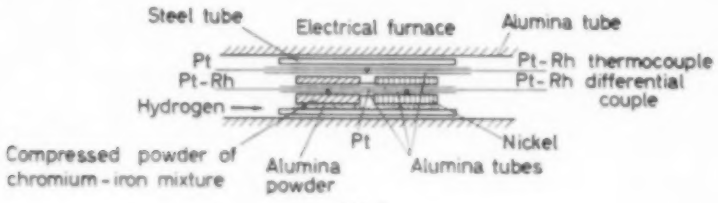

Abb. 1

Mischung von Chrom- und Eisenpulver, werden zusammen in einem elektrischen Ofen erhitzt. Durch die zentralen Bohrungen führt ein differentielles Pt/Pt–Rh Thermoelement mit je einer Schweißstelle in den beiden Metallzylindern. Die Temperaturdifferenz der Schweißstellen wird mit einem empfindlichen Spiegelgalvanometer gemessen. Ein weiteres Thermoelement dient zur Messung der Temperatur zwischen den Zylindern. Die Anordnung wird in etwa 80 min auf 1100°C erhitzt, und die Temperatur dann konstant gehalten; der Galvanometerausschlag wird derweil beobachtet, bis er auf Null zurückgegangen ist. Er ist in *Abb. 2* gegen eine Zeit–Temperatur–Skala aufgetragen. Am folgenden Tage wird das Experiment mit der gleichen Temperatur–Zeit-Folge wiederholt: die gestrichelt gezeichneten Galvanometerausschläge wurden beobachtet. Die Differenz der Galvanometerausschläge vom ersten und zweiten Versuch ist im unteren Teil der *Abb. 2* aufgetragen. Schliesslich wurde durch Mikrohärtemessungen festgestellt, dass sich der Chrom–Eisen–Pressling zu einer 50-prozentigen Legierung homogenisiert hatte.

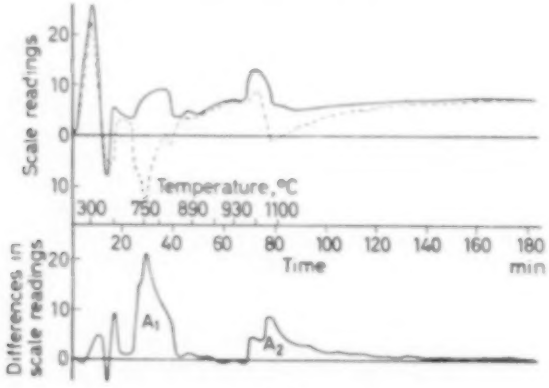

Abb. 2

Durch die Differenzbildung der Ausschläge werden im Idealfall alle Wärmeeffekte, die sich am zweiten Tage wiederholen, wie die magnetische

Umwandlungswärme von Nickel bei etwa 350°C, eliminiert. Im vorliegenden Falle sollten jedoch die Effekte unter 500°C wegen der schnellen Aufheizgeschwindigkeit ausser Acht gelassen werden. Die magnetische Umwandlung von Eisen erscheint als positiver Wärmeeffekt zwischen 680 und 880°C, da dieser nur im unlegierten Zustand auftritt: in der Legierung erscheint er als negativer Effekt bei etwa 500°C. Bei etwa 940°C macht sich die A3 Umwandlung des Eisens bemerkbar, und anschliessend verläuft über 1000°C die Bildungsreaktion ab. Die Bildung der Chrom–Eisen-Legierung ist demnach eindeutig endotherm. Die Grössenordnung des Effektes lässt sich durch Vergleich mit den beiden Eisenumwandlungen aus deren Umwandlungswärmen zu $+250 \pm 100$ cal/g-atom für die Bildung aus Cr und γ-Fe abschätzen, in Übereinstimmung mit einem kürzlich von G. Heymer bei uns aus Dampfdruckmessungen erhaltenen Wert.

Für genaue Messungen ist diese Anordnung ungeeignet. Ein im Prinzip ähnlich arbeitendes, etwas genaueres Calorimeter wurde von Fischer und Lorenz zur Untersuchung der Bildungsreaktion des Spinells $FeO{\cdot}Al_2O_3$ konstruiert[5]. Bei uns wurde von Dench und Genta[6] ein Hochtemperaturcalorimeter gebaut, das zur Bestimmung kleiner Reaktionswärmen bis zu einer Temperatur von 1000°C geeignet ist: *Abb. 3.*

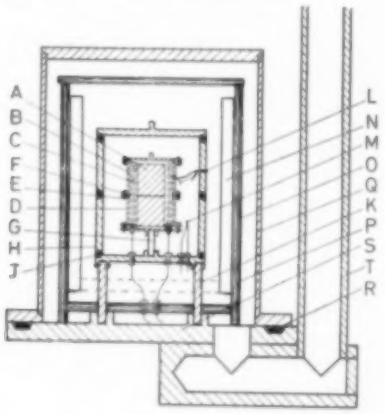

Abb. 3

Der zylindrische Pressling (A) befindet sich mit einem Platinöfchen (D) in einer Hülle (E) aus zunderfestem Stahl, die in je eine Boden- und Deckelplatte und zwei geflanschte Rohre unterteilt ist. Eine äussere Hülle (H) ist ebenso unterteilt, und die Einzelteile der inneren und äusseren Hülle sind mittels Sinterkorundröhrchen (F, J) voneinander isoliert. Die Auflagerohre bei G und K sind ebenfalls aus Sinterkorund. Vier hintereinandergeschaltete Pt/Pt–Rh Differential-Thermoelemente (L) haben je eine Schweißstelle auf einem Teilstück der inneren Hülle, die andere an dem entsprechenden Teilstück der äusseren. Sie sind mit einem Spiegelgalvanometer verbunden. Das Thermoelement M hat seine Heisslötstelle zwischen den beiden Hüllen.

Die Apparatur wird zunächst mit Hilfe einer Öldiffusionspumpe bei T evakuiert, und der Molybdändrahtofen (N) dann auf eine Temperatur

erhitzt, bei der sich die Metallpulver (z.B. Gold und Nickel) gerade noch nicht legieren, aber entgasen lassen. Danach wird der Ofen schnell auf die Temperatur gebracht, bei der sich die Pulver innerhalb etwa zwei Stunden (Vorversuche!) vollständig legieren. Die Spannung wird mit einem Stabilisator konstant gehalten. Die Galvanometerausschläge werden beobachtet, bis sie einen konstanten Wert erreichen. Dieser Wert ist nicht genau Null, weil sich ein (konstanter) vertikaler Temperaturgradient innerhalb der Hüllen nicht ganz vermeiden lässt.

Nach dem Abkühlen des Ofens wird das Experiment wiederholt, ohne irgendwelche äussere Veränderungen vorzunehmen. Wie *Abb.* 4 zeigt, wird der konstante Ausschlag diesmal schneller erreicht. Der Unterschied der beiden Kurven rührt von dem Wärmeverbrauch der Reaktion

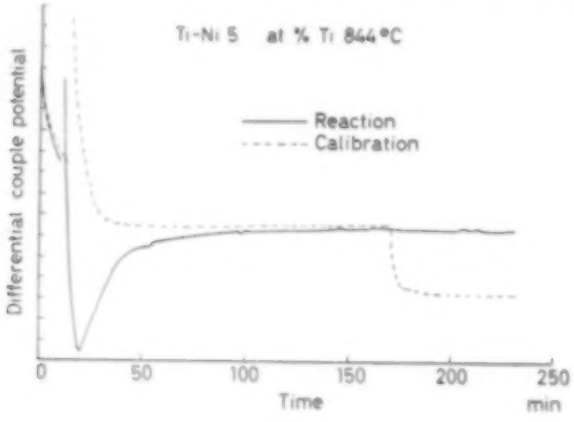

Abb. 4

her. Zur Eichung der entsprechenden Fläche wird der Platinofen (D) für ein gemessenes Zeitintervall mit einem konstanten Gleichstrom gespeist und Spannung und Stromstärke auf Präzisionsinstrumenten verfolgt. Aus dem Energieäquivalent der entsprechenden Fläche (*Abb. 4*) lässt sich schliesslich das Energieäquivalent der Fläche zwischen der Versuchs- und Eichkurve berechnen. Eine Unsicherheit der Auswertung ist dadurch bedingt, dass die Reaktion bereits einsetzt, bevor die Anordnung konstante Temperatur erreicht hat. Zur Kontrolle wurde die Eichung deshalb gelegentlich während des letzten Stadiums der Aufheizung vorgenommen: bei gleicher Energiezufuhr ergab sich der gleiche Flächeninhalt wie nach Einstellung des Gleichgewichtes.

In dem vorliegenden Beispiel der Bildung einer Gold–Nickel-Legierung mit 30 At.-Prozent Au ergab sich die Enthalpie zu 1190 $\pm$100 cal/g-atom. Für entsprechende Versuche mit Cu–Ni-Legierungen war die Übereinstimmung mit unabhängigen Messungen[7] gut.

Für spontan verlaufende Bildungsreaktionen ist dieses Calorimeter ungeeignet. Wir hatten deshalb einen Apparat[8] konstruiert, der sich für spontane Bildungsreaktionen insbesondere der Aluminide von Übergangsmetallen als brauchbar erwiesen hat. Hier möge eine knappe Beschreibung des Calorimeteres (*Abb. 5*) genügen.

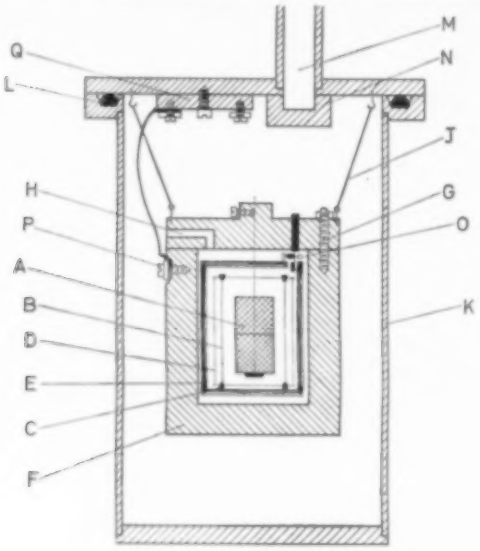

Abb. 5

Der Pressling (A) aus dem Metallpulver-Gemisch befindet sich in einem Molybdänofen (B), dessen Wärme durch eine Anzahl von Nickel–Strahlschilden (E) auf den Pressling konzentriert wird, in einem Aluminiumblock (F) mit Gasauslässen (H), der in einem Messingbehälter (K) hängt (J). Der Behälter steht in einem Thermostaten von 25,00°C. Zehn nacheinander geschaltete, differentielle Thermoelemente messen die Temperaturdifferenz zwischen dem Aluminiumblock (F) und dem Messingbehälter (Q).

Wenn ein Pressling, z.B. aus Mangan- und Aluminiumpulver, in F aufgehängt und der Behälter durch M evakuiert ist, wird der Ofen (B) elektrisch geheizt, während die zugeführte Energie mit einem Wattstundenmesser genau bestimmt wird. Die spontane Legierungsbildung macht sich durch einen plötzlichen Temperaturanstieg (z.B. bis 1050°C) bemerkbar. Der Ofen wird abgeschaltet und die Potentialdifferenz–Zeit–Kurve aufgenommen (*Abb. 6*). Um eine Wasserwertbestimmung des Calorimeters zu umgehen, wird die beschriebene Prozedur am folgenden Tage wiederholt, und zwar unter Zuführung von soviel elektrischer Energie, dass die Kurve des Vortages genau reproduziert wird. Zwei oder drei Eichversuche sind u.U. notwendig. Die Bildungswärme der Legierung ergibt sich dann einfach als Differenz der elektrischen Energiezufuhren am zweiten und ersten Tage. Die physikalischen Fehler werden damit auf die Messgenauigkeit des Wattstundenmessers reduziert. Die chemischen Fehler, wie Unvollständigkeit der Reaktion und der Effekt von Verunreinigungen, sind natürlich die gleichen wie bei allen derartigen calorimetrischen Messungen an Legierungen. Sie werden durch nachfolgende Analysen, mikroskopische und röntgenographische Untersuchungen weitgehend unter Kontrolle gebracht. Die Bildungswärme einer Legierung Mn_4Al_{11} ergab sich z.B. zu -5100 ± 200 cal/ g-atom.

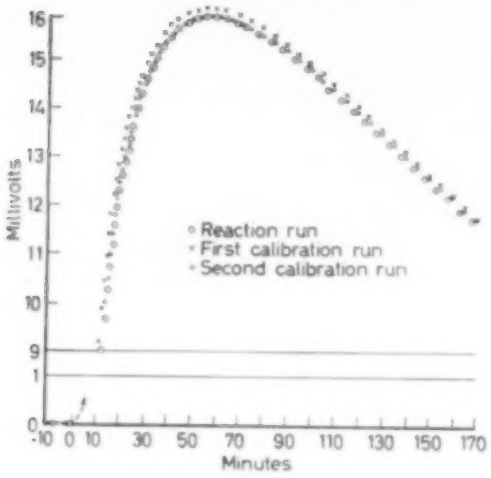

Abb. 6

Zu den metallurgisch wichtigen Substanzen gehören natürlich auch stärker exotherme, wie die Halogenide. Ihre Bildungswärme lässt sich im allgemeinen gut mit Hilfe der Lösungscalorimetrie in Säuren ermitteln. Die Methode ist jedoch weniger geeignet für das Studium kovalenter Halogenide mit niedrigem Siedepunkt. Direkte Verfahren sind auch hier vorzuziehen. Eine Calorimeterbombe für Chlorierungen wurde von Siemonsen[9] beschrieben. Gross, Hayman und Levi[10] haben ein elegantes Verfahren zur Bestimmung der Bildungswärme von Titantetrachlorid angegeben. Fräulein Dr von Goldbeck hat bei uns zur Untersuchung von Vanadintetrachlorid einen anderen Weg gewählt, der hier abschliessend beschrieben sein möge: *Abb. 7.*

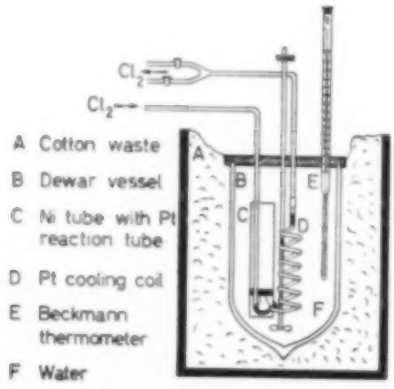

Abb. 7

Ein Platinrohr (Durchmesser 5 mm) in einem gewöhnlichen Wassercalorimeter, bestehend aus Beckmannthermometer, Rührer und Dewar-

VOL. 2 1961

gefäß, ist auf der Eingangsseite durch ein Nickelrohr von dem Calorimeterwasser getrennt und auf der Ausgangsseite spiralförmig gewunden, um eine grosse Oberfläche zu schaffen. Das Einlassrohr hat unten ein gebogenes Stück zur Aufnahme der Vanadinkügelchen und ist äusserlich mit einer Lage aus Bleiglas versehen, auf die 10 cm Cr–Ni-Draht gewunden sind. Zur Messung wird ein Chlorstrom durch das Platinrohr geleitet und dann der Cr–Ni-Draht mit einer genau gemessenen Elektrizitätsmenge für 6 min auf etwa 500°C geheizt. Das gebildete flüchtige VCl_4 kondensiert sich in der Spirale, und die gemessene Temperaturerhöhung stammt lediglich von der Bildungswärme des Tetrachlorids und der elektrisch zugeführten Energie. In den geschilderten Versuchen war der Anteil der elektrisch zugeführten Energie an der Gesamtwärmemenge, wie *Abb. 8* zeigt (untere Kurve), relativ beträchtlich. Bei zukünftigen Anwendungen der Methode sollte dieser Anteil möglichst herabgesetzt werden. Die Menge des gebildeten Tetrachlorids muss nach jedem einzelnen Versuch bestimmt und eine Korrektur für das vom Chlorstrom herausgeführte Chlorid berücksichtigt werden.

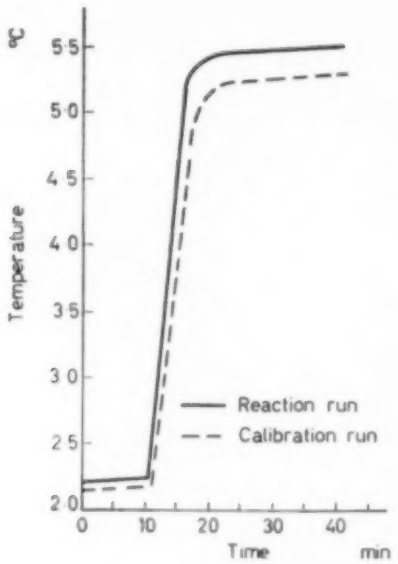

Abb. 8

Bei unseren calorimetrischen Arbeiten erwies sich stets die physikalische Seite der Messtechnik als das geringere Problem. Die Hauptfehlerquellen kamen von einer ungenügenden Beherrschung der chemischen Reaktionen und Nebenreaktionen her, ein Punkt, der leider nicht immer genügend beachtet wird: es wird nicht selten mit Kanonen nach Spatzen geschossen, d.h. ein grosser physikalischer Aufwand wird getrieben, um eine Genauigkeit zu erzielen, die auf der chemischen Seite keineswegs gerechtfertigt erscheint. Der Thermochemiker muss in erster Linie auch Analytiker sein: eine

Voraussetzung, auf die seinerzeit W. A. Roth immer wieder hingewiesen hat.

Die vorliegende Arbeit ist im Rahmen des Versuchsprogramms des National Physical Laboratory ausgeführt worden und wird mit Erlaubnis des Direktors des Laboratoriums veröffentlicht.

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VOL.
2
1961

ZUR THERMOCHEMIE VON LEGIERUNGEN

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Zur Ergänzung bekannter Verfahren zur Bestimmung thermodynamischer Kenngrössen von Legierungen[1] wurden folgende Möglichkeiten experimentell geprüft:

(1) Direktkalorimetrische Vereinigung der Komponenten
   (a) mit Fe–S–Gemisch (50 At. prozent) als Zündmaterial
   (b) durch Zündung mit einem in das Kalorimeter fallenden Heizkörper definierten Wärmeinhalts (" drop-Methode ").

(2) Indirekte Bestimmung von ΔG, ΔH und ΔS durch Bestimmung des Löslichkeitsproduktes der Phase $Me_x^I Me_y^{II}$ in einem Lösungsmetall Me^L bei verschiedenen Temperaturen.

Die Verfahren (1a) und (1b) kommen im wesentlichen in Frage bei relativ niedrig (unter 1000°C) schmelzenden Phasen. Verfahren 2 dagegen bietet Vorteile bei hochschmelzenden Verbindungen.

Zu (1a)—Bestimmt wurde die Bildungsenthalpie von InSb (Schmelzpunkt 525°C). Wasserwert des Kalorimeters: 3317 ± 13 cal. Zündgemisch: Eisen–Schwefel (50 At.-Prozent) $\Delta H^{B}_{298°K}(FeS) = -23{,}2 \pm 0{,}1$ kcal/Mol.

Das In–Sb-Gemisch (jeweils 12–17 g der stöchiometrischen Zusammensetzung InSb) wurde in einem Eisentiegel (etwa 25 mm hoch, 13 mm lichte Weite, 0,3 mm Wandstärke) luftdicht untergebracht. Einbettung des Tiegels in die Fe–S-Mischung: jeweils 15 g ≃ 3850 cal. Die zur Zündung aufgewendete Wärmemenge beträgt damit etwa das 10-fache der Reaktionswärme bei der Bildung von InSb.

Die Fehlerdiskussion ergibt: die kalorimetrisch ermittelte Gesamt-Wärmetönung ist mit einem Fehler von maximal ± 1,4 Prozent behaftet (Summe der Fehler bei der Bestimmung der Zündenergie, des Wasserwertes sowie des Umsatzgrades, der analytisch und metallographisch ermittelt wurde). Durch Differenzbildung wird der Fehler von ΔH(InSb) jedoch wesentlich erhöht: mittlere Abweichung vom Mittel bei sieben Messungen rund 8 Prozent. $\Delta H^{B}_{298°K}(InSb) = -3{,}4 \pm 0{,}3$ kcal/g-atom.

Zu (1b)—Bestimmt wurde die Bildungsenthalpie der Phasen $MgZn_2$, Mg_2Zn_{11} und MgZn. Schmelzmaximum im System Mg–Zn bei 590° und der Phase $MgZn_2$. MgZn und Mg_2Zn_{11} schmelzen unter Zersetzung bei 354° bzw. 380°. Gepresste Mischungen von Mg- und Zn-Pulver (jeweils 33 At. prozent Mg) reagieren rasch oberhalb 370° unter Legierungsbildung. Im Kalorimeter (Wasserwert: 4300 ± 8 cal) untergebrachte Mg–Zn-Presslinge werden zur Reaktion gebracht mit Hilfe eines von definierter Temperatur in das Kalorimeter über den Pressling fallenden Al_2O_3-Tiegels. Ofentemperatur zur Aufheizung des Tiegels: 950 ± 0,5°C. Fallzeit des

Tiegels nach Einschwenken des Ofens über das Kalorimeter: 0,2 sec. Gewicht des Al_2O_3-Tiegels: 20,818 g. Eichung mit Ag-Zylinder von 124,92 g = 4518 cal (zwischen 25° und 630°C). Einfallen des Al_2O_3-Tiegels von 950° entspricht einer notwendigen "Zündenergie" von rund 5000 cal (Fehler: ± 0,2 Prozent). Damit wird die Wärmetönung der Legierungsbildung zu rund 10 Prozent des gesamten kalorimetrischen Effektes. Wegen der guten Reproduzierbarkeit aller kalorimetrischen Manipulationen liegt trotz der ungünstigen Differenzbildung der Fehler der Bildungsenthalpie für $MgZn_2$ ($\Delta H_{298°K}$ = 3,6 kcal/g-atom) unter 7 Prozent (= ± 0,25 kcal). Entscheidend ist die Genauigkeit der Umsatzbestimmung, die wir chemisch, metallographisch und insbesondere röntgenanalytisch durchführten: Intensitätsmessung mit einem Röntgen-Diffraktometer ("Norelco" der Fa. Müller, Hamburg). Es gelingt, neben hauptsächlich gebildetem $MgZn_2$ auch geringe Anteile MgZn und Mg_2Zn_{11} quantitativ zu erfassen. Nicht umgesetztes Magnesium wurde durch Grignardierung erfasst. Die so ermittelte Menge Mg steht in Übereinstimmung mit dem Ergebnis der Röntgenanalyse. Ein graphisches Verfahren (Dreieckskoordinaten für prozentuale Anteile des Gemisches MgZn + $MgZn_2$ + Mg_2Zn_{11} mit ΔH-Ordinate) erlaubt aus mindestens drei kalorimetrischen Bestimmungen und genauer Analyse der Reaktionsprodukte (MgZn, $MgZn_2$, Mg_2Zn_{11} neben Mg und Zn) die Ermittlung der Bildungsenthalpien aller drei Mg–Zn-Phasen. Bei einer Einwaage von Mg : Zn = 1 : 2 (= 33 At.-Prozent Mg) ist allerdings der Fehler für ΔH(MgZn) bzw. $\Delta H(Mg_2Zn_{11})$ wegen der kleinen Menge der bei der Umsetzung gebildeten Phase grösser. Wir fanden:

$$\Delta H_{298°K}(MgZn_2) = 3{,}6 \pm 0{,}25 \text{ kcal/g-atom}$$

$$\Delta H_{298°K}(MgZn) = 2{,}5 \pm 0{,}75 \text{ kcal/g-atom}$$

$$\Delta H_{298°K}(Mg_2Zn_{11}) = 2{,}4 \pm 0{,}6 \text{ kcal/g-atom}$$

Bei genügend niedrig liegenden Reaktionstemperaturen bzw. genügend hohen Bildungsenthalpien erscheint das Verfahren auf eine Reihe anderer metallischer Systeme anwendbar: z.B. Mg–Sb, Ca–Sb, Mg–Ni, Ca–Al, Ce–Al, La–Al, Mg–Cu, Fe–Si *etc.*

Zu (*2*)—Bestimmt wurden ΔG, ΔH und ΔS für die Phasen Fe_2Zr, Al_4Zr_3, Al_3Zr_2 und Al_2Zr. Messprinzip: Bestimmung der Löslichkeitsprodukte der schwerlöslichen Phasen in flüssigem Magnesium als Lösungsmetall bei verschiedenen Temperaturen. Die Bestimmung von Sättigungskonzentrationen der reinen Komponenten (Fe, Al, Zr) bzw. der Phasen im Lösungsmetall (Mg) liefert in analoger Weise wie Dampfdruckmessungen ΔG-Werte, ist aber apparativ einfacher und bietet Vorteile insbesondere für hochschmelzende Phasen.

Wie Hume-Rothery erstmals zeigte, kann die Ausfällung einer festen metallischen Phase (z.B. Mg_2Si) aus festen oder flüssigen metallischen Lösungen formal genau so beschrieben werden wie die Fällung schwer löslicher Verbindungen aus wässriger Lösung. Das Löslichkeitsprodukt für Mg_2Si (gefällt aus Al als Lösungsmittel) ist

$$L = a^2_{Mg} \, a_{Si}$$

VOL. 2 1961

Logarithmierung ergibt allgemein für die Fällung von $Me^{I}_{x}Me^{II}_{y}$

$$\log a_{Me^{I}} = 1/x \,.\, \log L - y/x \,.\, \log a_{Me^{II}}$$

d.h. $\log a_{Me^{I}}$ gegen $\log a_{Me^{II}}$ aufgetragen gibt eine Gerade, deren Steigung durch den Richtungskoeffizienten y/x gegeben ist.

Nimmt man bestimmte Voraussetzungen als gegeben an:

(a) keine Moleküle der intermetallischen Phase in der Schmelze (berechtigt in sehr verdünnter Lösung);
(b) homogene und atomare Verteilung von Me^{I} und Me^{II} im Lösungsmetall Me^{L};
(c) Gültigkeit des Henry'schen Gesetzes (bei Me^{I}- bzw. Me^{II}-Konzentrationen unter rund 1 prozent);
(d) Phasengleichgewichte zwischen Me^{L}-Schmelze und fester $Me^{I}_{x}Me^{II}_{y}$ Phase,

so ergibt die Konode Me^{L}–$Me^{I}_{x}Me^{II}_{y}$ die Sättigungskonzentration für die Phase im flüssigen Me^{L} und log $[Me^{I}]$ gegen log $[Me^{II}]$ die Fällungsgerade.

Der Vorgang der Fällung aus dem Lösungsmetall Me^{L} ($\langle\ \rangle$ = feste Phase; $[Me^{I}]_{L}$ = Lösung von Me^{I} in flüssigem Me^{L}; $\Delta\overline{G}$ = partielle freie Enthalpie; ΔG = integrale freie Enthalpie):

$$x[Me^{I}]_{L} + y[Me^{II}]_{L} \rightleftharpoons \langle Me^{I}_{x}Me^{II}_{y}\rangle + \Delta\overline{G}^{B}_{Ph} \qquad (1)$$

ist mit der Energieumsetzung $\Delta\overline{G}^{B}$ verbunden: freie Bildungsenthalpie der Phasenbildung aus in Me^{L} gelösten Komponenten. $\Delta\overline{G}^{L}(= -\Delta\overline{G}^{B})$ ist entsprechend die freie Enthalpie der Überführung von 1 Mol $\langle Me^{I}_{x}Me^{II}_{y}\rangle$ in die verdünnte Lösung.

Zur Bestimmung der freien Bildungsenthalpie von $\langle Me^{I}_{x}Me^{II}_{y}\rangle$ aus den festen reinen Komponenten $x\langle Me^{I}\rangle$ und $y\langle Me^{II}\rangle$ führt folgender Zusammenhang:

$$\begin{array}{rl}
x\langle Me^{I}\rangle \rightleftharpoons x[Me^{I}]_{L} & + x\Delta\overline{G}^{L}_{Me^{I}} \\
y\langle Me^{II}\rangle \rightleftharpoons y[Me^{II}]_{L} & + y\Delta\overline{G}^{L}_{Me^{II}} \\
x[Me^{I}]_{L} + y[Me^{II}]_{L} \rightleftharpoons \langle Me^{I}_{x}Me^{II}_{y}\rangle & + \Delta\overline{G}^{B}_{Ph} \\
\hline
x\langle Me^{I}\rangle + y\langle Me^{II}\rangle \rightleftharpoons \langle Me^{I}_{x}Me^{II}_{y}\rangle & + \Delta G^{B}_{Ph}
\end{array}$$

Allgemein wird damit

$$\Delta G^{B}_{Ph} = \Delta\overline{G}^{B}_{Ph} + x\Delta\overline{G}^{L}_{Me^{I}} + y\Delta\overline{G}^{L}_{Me^{II}} \qquad (2)$$

In realer Lösung und im Henry'schen Bereich ($a = fN = \text{const.}\ N$) gilt unter Verwendung der Aktivitäten*

$$\Delta G^{B}_{Ph} = RT \ln a'^{x}_{Me^{I}}\, a'^{y}_{Me^{II}} - xRT \ln a''_{Me^{I}} - yRT \ln a''_{Me^{II}} \qquad (3)$$

* Hierbei sind a', c' = Aktivität bzw. Konzentration für gesättigte Schmelze über der Phase; a'', c'' = Aktivität bzw. Konzentration für gesättigte Schmelze über den reinen Komponenten.

$$\Delta G^{\mathrm{B}}_{\mathrm{Fb}} = RT(x \ln c'_{\mathrm{Me}\,\mathrm{I}} f_{\mathrm{Me}\,\mathrm{I}} + y \ln c'_{\mathrm{Me}\,\mathrm{II}} f_{\mathrm{Me}\,\mathrm{II}} - x \ln c''_{\mathrm{Me}\,\mathrm{I}} f_{\mathrm{Me}\,\mathrm{I}} - y \ln c''_{\mathrm{Me}\,\mathrm{II}} f_{\mathrm{Me}\,\mathrm{II}}) \quad (4)$$

$$\Delta G^{\mathrm{B}}_{\mathrm{Fb}} = RT\, x \ln \frac{c'_{\mathrm{Me}\,\mathrm{I}} f_{\mathrm{Me}\,\mathrm{I}}}{c''_{\mathrm{Me}\,\mathrm{I}} f_{\mathrm{Me}\,\mathrm{I}}} + RT\, y \ln \frac{c'_{\mathrm{Me}\,\mathrm{II}} f_{\mathrm{Me}\,\mathrm{II}}}{c''_{\mathrm{Me}\,\mathrm{II}} f_{\mathrm{Me}\,\mathrm{II}}} \quad (5)$$

$$= RT\, x \ln c'_{\mathrm{Me}\,\mathrm{I}}/c''_{\mathrm{Me}\,\mathrm{I}} + RT\, y \ln c'_{\mathrm{Me}\,\mathrm{II}}/c''_{\mathrm{Me}\,\mathrm{II}} \quad (6)$$

$$\Delta G^{\mathrm{B}}_{\mathrm{Fb}} = RT \ln c''_{\mathrm{Me}\,\mathrm{I}}\, c''_{\mathrm{Me}\,\mathrm{II}} - RT(x \ln c''_{\mathrm{Me}\,\mathrm{I}} + y \ln c''_{\mathrm{Me}\,\mathrm{II}}) \quad (7)$$

Sind demnach für mindestens zwei Temperaturen bekannt (a) das Löslichkeitsprodukt der Phase und (b) die Sättigungskonzentrationen der reinen Komponenten im Lösungsmetall Me^{L}, so sind ausser $\Delta G^{\mathrm{B}}_{\mathrm{Fb}}$ auch $\Delta H^{\mathrm{B}}_{\mathrm{Fb}}$ und $\Delta S^{\mathrm{B}}_{\mathrm{Fb}}$ zu berechnen.

Hierbei können in Gleichung (7) unmittelbar die analytisch bestimmten Konzentrationen eingesetzt werden. Da Sättigungskonzentrationen meist mit guter Genauigkeit (*Temperaturfehler* $<0{,}1$ *Prozent; Analysenfehler* $<1{,}0$ *prozent*) zu ermitteln sind, liegen die Fehler der berechneten ΔG-, ΔH- und ΔS-Werte nicht wesentlich über 5–10 Prozent, sofern echte Gleichgewichte gemessen werden. Das wiederum ist relativ leicht sicherzu stellen durch (a) Ausfällen der Phase und (b) Lösen im Me^{L} und Vergleich der erzielten Sättigungskonzentrationen.

Die von uns bestimmten Werte sind:

$\mathrm{Fe_2Zr}$: $\Delta G^{\mathrm{B}}{}_{(\mathrm{Fe_2Zr})}$ = molare freie Bildungsenthalpie aus den festen Komponenten $= -17700 + 5{,}2\ T$ cal/Mol

$= -7{,}6 \pm 0{,}5$ kcal/g-atom (750°)

$\Delta H = -17{,}7 \pm 1{,}0$ kcal/Mol

$\Delta S = 5{,}2$ cl/Mol

$\mathrm{Al_2Zr}$: $\Delta G^{\mathrm{B}} = -13{,}6$ kcal/g-atom

$\mathrm{Al_3Zr_2}$: $\Delta G^{\mathrm{B}} = -12{,}8$ kcal/g-atom

$\mathrm{Al_3Zr_4}$: $\Delta G^{\mathrm{B}} = -10{,}3$ kcal/g-atom

Literatur

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VOL. 2 1961

THE USE OF REACTION CALORIMETRIC METHODS FOR MEASURING HEATS OF FORMATION OF ORGANO-METALLIC COMPOUNDS

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The measurement of the heats of formation of organo-metallic compounds presents, usually, a difficult task to the experimental thermochemist. Thus the method of combustion in a conventional bomb-calorimeter, although it has been applied to a number of metallic alkyls in recent years[1] and yielded valuable results, is nevertheless not entirely satisfactory. The difficulty is that complete oxidation of the organo-metallic compound is not always attained, and the metal may be left, after the combustion, in a partially oxidized state, as a mixture of free metal, oxides, and possibly carbonate and carbide. The development of the rotating-bomb technique offers a solution of this major difficulty, and successful studies have already been reported by Scott, Good and Waddington[2] on the combustion of lead tetraethyl, and by Good, Fairbrother and Waddington[3] on manganese carbonyl. One can therefore feel confident that in due course precision measurements of combustion heats of organo-metallic compounds will be made.

However, it is desirable that methods other than that of combustion should be investigated, not only to provide independent checks on combustion results, but also to develop reaction calorimetric methods. Several typical reactions of organo-metallic compounds are potentially suitable for heat of formation measurements, but comparatively few such thermal studies have as yet been made. Some of these studies are briefly discussed below.

HYDROLYSIS REACTIONS

Several of the alkyls of the metals belonging to Groups I, II, and III are easily hydrolysed by water, or by dilute acids, at room temperature. Measurements of heats of hydrolysis are available for cadmium dimethyl, cadmium diethyl, zinc dimethyl, and zinc diethyl, from which heats of formation have been derived[4]. It should be possible to extend studies of this type to the alkyls of the alkali metals and the alkaline earths, to beryllium alkyls, and the alkyls of aluminium and gallium. Apart from manipulative and preparative difficulties, the main problem is that of controlling the vigour of the hydrolysis reactions. In this connection, the studies already made on the hydrolysis of zinc and cadmium alkyls could be improved upon by hydrolysis in a diluent solvent.

HALOGENATION REACTIONS

Many metallic alkyls readily react with halogens, and in suitable cases these reactions can be studied thermochemically, and so provide useful heat of formation data. Examples already investigated include the iodination of cadmium dimethyl and diethyl, the iodination of zinc diethyl[4], and the iodination of gallium trimethyl[5]. Thermochemical studies on the iodination and bromination of a number of mercury dialkyls[6] have been made *via* the pairs of reactions (X = Br, or I):

$$HgR_2 + X_2 \rightarrow HgRX + RX \qquad \text{(i)}$$

$$HgR_2 + HgX_2 \rightarrow 2HgRX \qquad \text{(ii)}$$

from which the heat of total halogenation:

$$HgR_2 + 2X_2 \rightarrow HgX_2 + 2RX \qquad \text{(iii)}$$

was derived.

Table 1 summarizes the heat of formation data on metal alkyls obtained by these reaction calorimetric studies: in the same table, the heats of formation derived from combustion heats are also given, where available, for purposes of comparison[7]. The agreement between the heats of formation derived from combustion and reaction calorimetric methods is very fair, although neither method has yet given results of high precision.

VOL. 2 1961

Table 1. Heats of formation of organo-metallic compounds

Compound	*Method*	ΔH_f°(kcal/mole)	
		Reaction calor.	*Combustion*
$CdMe_{2(l.)}$	Hydrolysis	+ 16·7 ± 0·5	+ 19·6 ± 3
$CdEt_{2(l.)}$	,,	+ 14·5 ± 0·5	—
$ZnMe_{2(l.)}$	,,	+ 6·3 ± 1	+ 6·5 ± 2
$ZnEt_{2(l.)}$	,,	+ 4·3 ± 1	+ 4·1 ± 3
$HgMe_{2(l.)}$	Bromination	+ 12·3 ± 2	+ 14·3 ± ?
$HgEt_{2(l.)}$	,,	+ 5·2 ± 2	+ 6·5 ± ?
$HgPr_{2(l.)}$	,,	− 8·6 ± 3	—
$Hg^iPr_{2(l.)}$	,,	− 3·8 ± 3	—
$HgPh_{2(c.)}$	Reaction with HCl	+ 65·4 ± 2	+ 66·9 ± 2
$GaMe_{3(l.)}$	Iodination	− 14·5 ± 8	− 17·6 ± 3

HEATS OF HYDROBORATION

Brown and Subba Rao[8] have recently reported that in the presence of organic ethers, diborane adds to olefins with remarkable ease and speed at room temperature to form organoboranes in high yields:

$$6\,RCH{=}CH_2 + B_2H_6 \rightarrow 2(RCH_2CH_2)_3B$$

Since the heats of formation of olefins and diborane are already known, the measurement of heats of hydroboration provide a route to the heats of formation of organoboranes.

J. E. Bennett and J. B. Pedley have recently made a preliminary series of measurements on the heats of addition of diborane to the olefins hex-1-ene,

oct-1-ene, and oct-2-ene, in diglyme ($CH_3(OCH_2CH_2)_2OCH_3$) solution. They used a silver-plated copper calorimeter containing a Pyrex glass reaction vessel immersed in water: the calorimeter was placed inside a metal jacket within a thermostat. The temperature of the calorimeter was measured by a shielded thermistor element (Stantel, F/2311/300) immersed in the calorimetric fluid.

The reaction vessel was similar in design to that used by Brown and Gintus[9] in their measurements of the heat of solution of diborane in various solvents. The diborane gas entered the reaction chamber (*Figure 1*) through the glass sinter, K, which was sealed with sufficient mercury ($\sim$1 cm^3) to allow the sinter to operate as a valve. The reaction chamber contained a known amount of diglyme–olefine solution (usually $\sim$28 cm^3) stirred at constant speed (136 rev/min) by a stainless steel stirrer through a ball and socket joint, A. The exit gases escaped through the filling tube, D, and passed into a water-containing trap outside the calorimeter, the purpose of which was to decompose any diborane gas escaping from the reaction vessel.

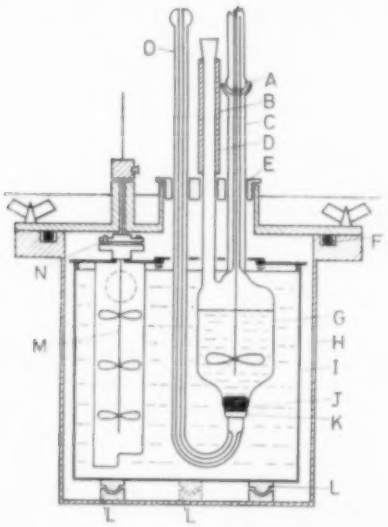

Figure 1. Calorimeter and reaction vessel: A, C, ball and socket joint: Pyrex capillary; B, small electric heater; D, exit tube; E, polythene spacers; F, O-ring seal; G, Pyrex reaction vessel; H, outer calorimeter jacket; I, silver-plated copper can; J, mercury; K, glass sinter; L, Bakelite pegs; M, stirrer; N, stirrer connection

The calorimeter can contained a propeller stirrer, M, located in a brass tube, an electric heater for calibration, and a shielded thermistor element: it was charged with 700 g of distilled water for each experiment, and sealed with a lid, slotted to take the inlet tubes of the reaction vessel and support it firmly in position. The can was supported by three bakelite pegs, L, inside a brass jacket, closed at the top by a flanged lid: the whole assembly was immersed in a water thermostat bath.

The experimental procedure was as follows.

The reaction vessel was cleaned and thoroughly dried, and swept out with dry nitrogen: it was then charged with a solution containing a known amount of pure diglyme and olefin, and placed in position in the calorimeter can. The calorimeter was located in the jacket, the flange-lid bolted on, and the assembly immersed in the thermostat. The calorimeter and reaction vessel stirrers were set in motion, and the calorimeter heater used to bring the calorimeter temperature within $\frac{1}{2}$°C of 25°C.

Before introducing the diborane in quantity, a small amount (usually 5–10 cm³) was passed through the filling lines (Pyrex capillary), *via* the mercury-sealed sinter into the diglyme solution: this "flushing" with diborane was intended to rid the filling lines of traces of moisture, and to destroy traces of moisture and other reactive impurities remaining in the diglyme solvent. The diborane flushing was immediately followed by a flushing with pure dry nitrogen. The system was then allowed time to regain a steady thermal state.

Thermistor resistance readings were recorded at regular intervals to establish the fore-rating period, following which the reaction proper was carried out, by introducing a measured volume (usually ~50 cm³) of diborane into the reaction vessel from a calibrated gas-burette. The reaction time was usually about 20 min. After introducing the diborane, the reaction vessel was again flushed out with dry nitrogen, and the after-rating thermistor readings recorded.

VOL
2
1961

Preparation of compounds

Diborane was prepared by treating sodium boron hydride with boron trifluoride-etherate, in diglyme solvent, as described by Brown and Rao[6]. The diborane gas was purified by low-temperature fractional distillation in an all-glass grease-free vacuum system. The diborane was freshly prepared before each experiment in quantities of ~100 cm³, sufficient for one experiment only.

Diglyme was supplied by the Ansul Chemical Company, and purified by distillation under reduced pressure (20 mm Hg) from lithium aluminium hydride. The purified stock solution was stored under dry nitrogen.

Hex-1-ene was a high-purity (99·9 per cent) sample, supplied by the Chemical Research Laboratory, D.S.I.R., Teddington.

Oct-1-ene and oct-2-ene were commercial samples (Light and Co.), purified by distillation from sodium and by fractional distillation.

Cyclohexene was similarly purified.

In the latter cases, the degree of purity of the hydrocarbons was not known, nor were purity measurements made.

Calibration

The calorimeter was calibrated electrically by the substitution method. The heat exchange between calorimeter and jacket during an experiment was evaluated from the time–temperature curves by the Regnault–Pfaundler method. From the spread in the measured calibration constants, the calorimeter performance was reproducible within limits of $\pm\frac{1}{4}$ per cent.

Units

Heat quantities are expressed in thermochemical calories, defined by 1 cal ≡ 4·1840 abs. joules. The measurements were made at 25°C.

In estimating the amount of diborane from the volume used, it was accepted that 1 mole of B_2H_6 at N.T.P. occupies 22·15 l.

Results

In order to test the calorimetric method, a number of measurements were made of the heat of hydrolysis of diborane gas. In these experiments, the reaction vessel was charged with 25 cm³ of pure water, and a measured volume of diborane was introduced into the vessel. Of the total diborane used, only 70–80 per cent was hydrolysed in the reaction vessel, the remainder being carried away by the effluent hydrogen gas and hydrolysed outside the calorimeter in the water-filled trap. The amount of diborane hydrolysed in the reaction vessel was determined from the amount of boric acid recovered from it after the experiment; similarly, the amount of boric acid formed in the water-trap measured the diborane escaping hydrolysis in the reaction vessel.

From a series of independent purity determinations, it was established that the average purity of the diborane used in these experiments was 98·9 per cent.

To calculate the heat of hydrolysis, it was necessary to define the amount of diborane hydrolysed *in the reaction vessel* in each experiment. This was done in two ways:

(1) from the amount of boric acid recovered from the reaction vessel;

(2) from the amount of diborane introduced into the reaction vessel, less that escaping from it, as determined by the amount of boric acid recovered from the water trap.

The two methods of estimating the amount of reaction generally agreed with one another within limits of 1 per cent, the mean of the two measures being accepted as correct.

It was assumed that the hydrogen gas formed in the reaction vessel was saturated with water vapour before escaping the calorimeter, and that an evaporation heat correction was necessary to allow for this effect. This amounted to 2·0 kcal/mole of diborane hydrolysed in the reaction vessel. The heat of hydrolysis results are summarized in *Table 2.*

Table 2. Heat of hydrolysis of diborane gas

Expt.	B_2H_6 *used* (m. moles)	B_2H_6 *hydrolysed in R.V.* (m. moles)	*Heat evolved* (cal)	$-\Delta H_{hydrol.}$ (kcal/mole of B_2H_6)
1	2·070	1·511	166·0	111·8
2	2·034	1·777	194·5	111·5
3	1·897	1·307	142·5	110·9
4	2·249	1·813	199·4	112·0
				Mean value = 111·5 ± 0·4

The overall uncertainty in the mean $\Delta H_{hydrol.}$ is appreciably greater than the spread of the observed results, if allowance is made for the accuracy

of the calorimeter ($\pm\frac{1}{4}$ per cent), and the uncertainty in analysis (*ca.* $\pm\frac{1}{2}$ per cent) of the amount of B_2H_6 hydrolysed in each run; nevertheless, the agreement with the value obtained by Prosen, Johnson and Pergiel[10], $\Delta H_{\text{hydrol.}} = -111{\cdot}46 \pm 0{\cdot}54$ kcal/mole, is most satisfactory.

Hex-1-ene

The reaction occurring with hex-1-ene in solution was presumed to be:

$$B_2H_{6(\text{gas})} + 6\ C_6H_{12(\text{diglyme, soln.})} \rightarrow 2\ B(C_6H_{13})_{3(\text{diglyme, soln.})} \qquad \text{(i)}$$

and the observed heat of reaction, $\Delta H_{\text{obs.}}$, refers to this reaction. It is important to stress that we have not established by analysis of the products that reaction (i) occurs without any contaminating side-reactions. We have considered the possibility of incomplete reaction, with the formation of $(C_6H_{13})_2BH_2B(C_6H_{13})_2$; however, addition of water to the reaction products did not result in a significant evolution of gaseous products, so that this possibility would seem to be eliminated. We have in all experiments used a large excess of hex-1-ene relative to diborane. The amount of diborane consumed by reaction (i) in each run was determined from the amount of diborane introduced into the reaction vessel, less that escaping and subsequently hydrolysed in the water-trap outside the calorimeter. Reaction (i) is extremely rapid, and only very small amounts of diborane gas were found to escape the reaction zone.

Measurements were made separately in a small Dewar vessel calorimeter of the heats of solution in diglyme of hex-1-ene, and of pure boron trihexyl. Solution heat corrections were made to $\Delta H_{\text{obs.}}$ in order to obtain ΔH_2 of the simple reaction:

$$B_2H_{6(g.)} + 6\ C_6H_{12(l.)} \rightarrow 2B(C_6H_{13})_{3(l.)} \qquad \text{(ii)}$$

In each experiment, a preliminary "flushing" of the reaction vessel and contents with diborane was carried out to remove traces of moisture. In some experiments, the diglyme solvent was pre-treated with diborane in the calorimeter before addition of hex-1-ene.

The results obtained are preliminary in nature, since we intend to repeat the investigation using a larger reaction vessel and a more precise calorimeter, and also to improve the present analytical technique. The details of a representative sample of the more satisfactory runs are given in *Table 3*.

Table 3. Heat of hydroboration of Hex-1-ene

	Run No.	1	2	3
B_2H_6 (m. moles)	(i) flush	0·457	0·405	0·477
	(ii) water-trap	0·015	0·005	0·008
	(iii) consumed	2·051	1·887	2·062
C_6H_{12} (m. moles)	(i) added	15·7	14·4	21·1
	(ii) consumed	12·3	11·3	12·3
$\Delta H_{\text{obs.}}$	(kcal/mole of B_2H_6)	− 137·4	− 135·9	− 137·7
$\Delta H_{\text{soln.}}$	(kcal/6 moles of C_6H_{12})	4·5	4·5	4·1
$\Delta H_{\text{soln.}}$	(kcal/2 moles of $B(C_6H_{13})_3$)	0·5	0·5	0·5
ΔH_2	(kcal/mole of B_2H_6)	− 133·4	− 131·9	− 134·1

The mean value, $\Delta H_2 = -133{\cdot}1$ kcal/mole, is subject to experimental error limits of *ca.* ± 2 kcal/mole, but the overall error limits may be larger than this in view of the assumptions made regarding the reaction which occurs. From the mean ΔH_2 value, we may derive $\Delta H_f^\circ(B(C_6H_{13})_{3(l.)}) = -114{\cdot}7$ kcal/mole, assuming the values $\Delta H_f^\circ(B_2H_{6(g.)}) = 7{\cdot}5$ kcal/mole (Wagman, Munson, Evans, and Prosen[11]), and $\Delta H_f^\circ(C_6H_{12(l.)}) = -17{\cdot}28$ kcal/mole (Camin and Rossini[12]).

Oct-1-ene, Oct-2-ene, Cyclohexene

The experiments on the octenes and cyclohexene have been less thorough than those on hex-1-ene, and we shall not present detailed results. In the case of oct-1-ene, the mean value of $\Delta H_{obs.} = -136{\cdot}6$ kcal/mole was almost the same as that obtained with hex-1-ene, and, corrected for the solution heats, gave $\Delta H_2 = -132{\cdot}6$ kcal/mole. The heat of reaction for oct-2-ene (a mixture of *cis*- and *trans*-isomers) was markedly less than that for oct-1-ene: we obtained $\Delta H_{obs.} \simeq -123$ kcal/mole, and $\Delta H_2 \simeq -118{\cdot}5$ kcal/mole. In the case of cyclohexene some precipitation of tricyclohexyl boron from diglyme solution occurred during the runs, and there was also some evidence of incomplete hydroboration. It seemed clear, however, that the heat of reaction with cyclohexene is much less (by $\sim$20 kcal/mole) than with hex-1-ene.

DISCUSSION

From heat of combustion studies, Prosen and Johnson[13] have derived $\Delta H_f^\circ = -83{\cdot}9$ kcal/mole for boron tributyl (liq.), and Haseley, Garrett and Sisler[14] reported $\Delta H_f^\circ = -75 \pm 6$ kcal/mole for boron tri-*sec*-butyl. From these data, in conjunction with the available values[11, 15] $\Delta H_f^\circ(B_2H_{6(g.)}) = 7{\cdot}5$ kcal/mole, $\Delta H_f^\circ(\text{but-1-ene}_{(l.)}) = -5{\cdot}09$ kcal/mole, $\Delta H_f^\circ(\textit{cis}\text{-but-2-ene}_{(l.)}) = -7{\cdot}12$ kcal/mole, and $\Delta H_f^\circ(\textit{trans}\text{-but-2-ene}_{(l.)}) = -7{\cdot}97$ kcal/mole, we may calculate the heats of the following reactions, which correspond to reaction (ii):

$$B_2H_{6(g.)} + 6\ \text{But-1-ene}_{(l.)} \rightarrow 2\ B(\text{n-Bu})_{3(l.)}\ \Delta H_{calc.} = -144{\cdot}8 \text{ kcal/mole}$$

$$B_2H_{6(g.)} + 6\ \textit{cis}\text{-But-2-ene}_{(l.)} \rightarrow 2\ B(\textit{sec}\text{-Bu})_{3(l.)}\ \Delta H_{calc.} = -114{\cdot}8\ (\pm 12) \text{ kcal/mole}$$

$$B_2H_{6(g.)} + 6\ \textit{trans}\text{-But-2-ene}_{(l.)} \rightarrow 2\ B(\textit{sec}\text{-Bu})_{3(l.)}\ \Delta H_{calc.} = -109{\cdot}7\ (\pm 12) \text{ kcal/mole}$$

In comparison, the value we have obtained for ΔH_2 with hex-1-ene and oct-1-ene is *ca.* 10 kcal/mole smaller than that calculated for reaction with but-1-ene; on the other hand, our value for ΔH_2 with oct-2-ene is *ca.* 10 kcal/mole larger than that calculated for reaction with but-2-ene. In the latter case, the difference is covered by the large error limits attached to the combustion heat measurements of Haseley *et al.*[14]. The discrepancy in the former case is not easily accounted for at this stage, but both our own measurements and those of Prosen and Johnson[13] are preliminary in character, and may be subject to revision later.

Note added in proof

A more complete account of the hydroboration studies will appear in *J. Chem. Soc.* in 1961. The final results differ somewhat from those given here, mainly in that corrections for the heats of solution of products have been more accurately measured.

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A PLASTIC CAPSULE TECHNIQUE FOR THE COMBUSTION CALORIMETRY OF VOLATILE OR CHEMICALLY REACTIVE COMPOUNDS: THE HEAT OF COMBUSTION OF POLYTHENE

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INTRODUCTION

A considerable number of compounds of current thermochemical interest are either volatile or chemically reactive or both. The precise calorimetry of such compounds is fraught with difficult technical problems. This is specially so for combustion heat studies in a bomb calorimeter. Here it is of vital importance:

(a) to prevent chemical change or contamination of the pure sample at any time prior to ignition;
(b) to prevent evaporation of the sample during the weighing process or thereafter;
(c) to ensure, in so far as may be compatible with (a) and (b), that the conditions for complete combustion of the sample are optimum.

There have been several approaches to these problems, but the most efficacious and widely used has been to introduce the substance (usually a liquid) into glass ampoules of suitable size and then to seal these[1–5]. Such sealed ampoules completely satisfy conditions (a) and (b) above, but they have a number of disadvantages. The technique of manufacturing and filling them requires considerable skill, and, even at best, is a hit-and-miss affair. They have to be strong enough to withstand the pressure (30–40 atm) of oxygen in the bomb without bursting and yet not so strong that they fail to break on ignition of the auxiliary burning substance. In general, they fail to satisfy condition (c) in that the risk of explosion and incomplete combustion is fairly high[3–5]. An ingenious way of minimizing these latter difficulties is due to Thompson[6]. Again, sealing of the ampoules is a very delicate operation since it is liable to cause a certain amount of decomposition of the sample. Finally, there is always the danger that the melting glass may occlude some intermediate products of the combustion, though apparently this does not in general occur to any significant extent[5].

The above considerations have led us to search for a straightforward and reliable alternative to the glass ampoule technique, and we believe we have found such in the following simple method for making closed polythene capsules of any desired size or shape.

EXPERIMENTAL PROCEDURE

The raw material for the method is polythene (Imperial Chemical Industries, Ltd "Alkathene") sheet 0·2 mm thick. This is heat-softened

and vacuum-formed round suitable brass moulds with the aid of the set-up illustrated in *Figure 1*(*a*). A is a cylindrical vacuum box fitted with a

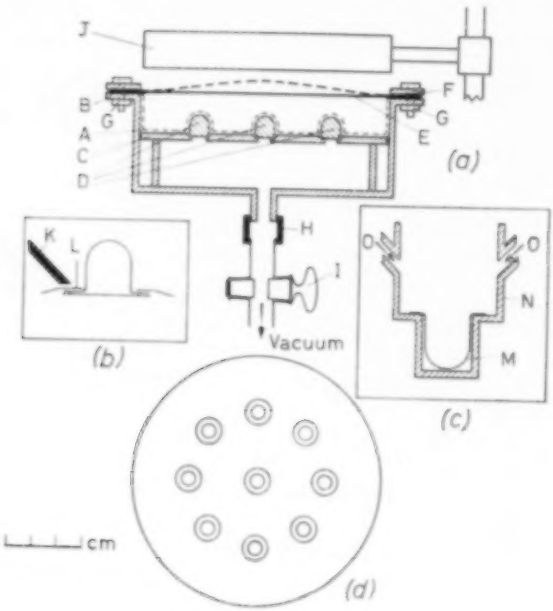

Figure 1

flange B. It is made of hard-drawn brass 1 mm thick. C is the brass platform carrying the nine moulds. It is a sliding-fit for A and is shown in plan in (*d*). The moulds, D, fit snugly into 1 cm-diameter grooves in the platform, as indicated. Under each mould is a 0·5 cm-diameter perforation. The polythene sheet E is clamped as a diaphragm on top of A with the aid of a flat ring F and four wing-nuts, two of which are shown at G. H is a piece of pressure tubing and I a glass tap. J is a 250 W heating element. We actually use an Osram infra-red lamp (I.R.R. 48 P.F.). It is mounted to swivel in the horizontal plane so that it may be swung quickly over and away from the polythene.

The procedure is as follows.

When all is ready the tap I is *closed* and the pump started. J is then switched on and swung into position about 3 cm directly above the diaphragm. Owing to the expansion of the air in the box the polythene swells up slightly as it is heated. This is indicated by the dotted line in *Figure 1*(*a*) and is an important feature of the method. Without this slight pressure build-up the softening polythene would sag down and foul the moulds before it is quite ready for vacuum-forming. The correct moment for removing the heat and applying the vacuum by opening tap I can be gauged easily by the eye: it is the moment at which the polythene has become quite transparent. On application of the vacuum, the poly-

thene quickly "forms" round the moulds as shown by the dotted line. The moulded sheet is then removed and the capsules cut out with a cork-borer of suitable diameter (1·5 cm). Polythene lids are heat-sealed on the capsules by applying a soldering iron K *via* a "Fluon"-coated glass cloth L, as indicated in *Figure 1(b)*.

The simplest method of charging the capsules with liquids is to use a hypodermic syringe. A small puncture is first made in the lid and the liquid injected through a second puncture. These punctures may then be sealed with a drop of molten polythene from a flaming piece of welding rod. It is quite easy with practice to seal the punctures with a mass of molten polythene that is small and reproducible within narrow limits. Its contribution to the heat output can thus be estimated reliably. For compounds which are susceptible to attack by atmospheric vapours or light, the above operations may be performed readily in an inert atmosphere, such as dry nitrogen, in a dark room. The capsules may be charged with volatile or reactive solids with the aid of the apparatus shown in *Figure 1(c)*. The capsule, M, without its lid, is placed in the brass container, N, as shown. The system is swept out with dry nitrogen *via* the two inlets, O. A suitable quantity of the solid sample is then transferred to M, the nitrogen counter-current being maintained the while. Finally, the lid is dropped into place and heat-sealed to the capsule as before.

The successful application of the present technique demands a precise knowledge of the heat of combustion of polythene. We have determined this under standard conditions with the apparatus described in an earlier paper[7]. The results are given in *Table 1* (1 cal = 4·1840 abs. joules).

Table 1. Heat of combustion of polythene

Vacuum weight of polythene (g)	*Total* (cal)	*I.C.** (cal)	*B.A.*† (cal)	*Polythene* (cal)	*Polythene* (kcal/g)
0·066484	− 3145·84	15·91	− 2423·47	− 738·28	11·105
0·092032	− 3460·87	16·44	− 2455·00	− 920·32	11·108
0·077026	− 3244·82	15·56	− 2404·89	− 855·49	11·107
0·065572	− 3105·87	15·83	− 2393·70	− 728·00	11·102
				Mean =	11·106
				Δ =	± 0·004

* I.C. = isothermal correction.
† B.A. = contribution to the total heat of the benzoic acid used as an auxiliary burning substance.

DISCUSSION

The present technique has obvious advantages over those involving glass, including even some of the most recent and elegant[5, 8, 9]. Among these advantages are the following:

(1) A large number of capsules almost identical in size, shape and weight can be made in a short space of time and without the need for any special skill.

(2) The size and shape of the capsules can be varied readily by changing the moulds.

(3) The capsules never burst before ignition as they are more than strong enough to withstand the pressure in the bomb.

(4) They are readily combustible and thus serve the purpose of an auxiliary burning substance, although they do not invariably eliminate the need for the latter.

(5) The fuse wires can be fixed at the neck of the capsules so that they have prolonged burning contact with the sample. The conditions for complete combustion are thereby enhanced.

(6) Polythene is resistant to attack by most chemicals at ordinary temperatures. The need, except in very special circumstances, for such as quartz ampoules[10] is thereby removed.

We thank Mr M. A. H. Lanyon, I.C.I. Ltd (Plastics Division) for valuable advice on the vacuum-forming procedure. R.G.M. is grateful to the Ministry of Education, N.I., for a Research Maintenance Grant.

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VOL. 2 1961

AN ADIABATIC CALORIMETER FOR MEASURING HEATS OF VAPORIZATION AT 25°C

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APPARATUS

The construction of the calorimeter is shown in *Figure 1*. The calorimeter body consists of five gold-plated brass discs (A–E). The substance to be vaporized is applied to a glass fibre wick (F) lying in the cavity between discs B and C. The wick is kept in a spiral form by means of a gold spiral (G). Through a gold tube (H) a slow stream of argon is forced over the wick. The heat loss accompanying the vaporization is compensated by electrical energy generated in the heating element (I), which is a spiralized manganin wire, lacquered and nylon-spun (40 Ω resistance) lying in a spiral grove in disc D. An air gap between disc D and the bottom disc E prevents overheating of the bottom surface. Discs A and B are fastened to C by means of four screws.

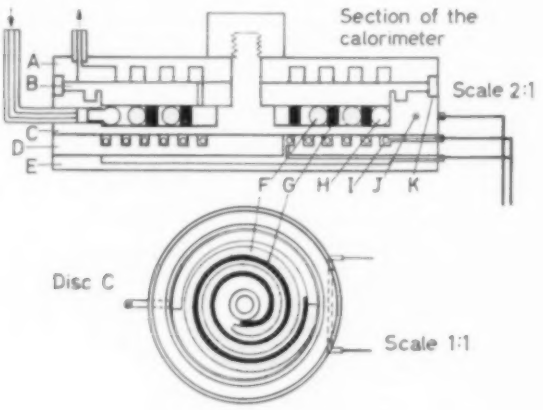

Figure 1

The saturated gas flows through the spiral in disc A so that the gas has attained the temperature of the calorimeter when it reaches the outlet tube. In the horizontal boring in disc C there is a thermistor (J) (Stanthel U2361/20, 2000 Ω) sealed in a 0·8 mm thin-walled glass tube. The electrical connections to heater and thermistor consist of 0·4 mm platinum wires dipping into mercury cups. To prevent substance leakage a silicon rubber gasket (K) is introduced between discs B and C.

The calorimeter is placed on three polystyrene pegs inside a chromium-plated brass can fitted with a lid. The can is placed in a bigger brass vessel which is immersed in a water thermostat. The space between the two cans is filled up by copper chips. The water thermostat is kept at 25·00°C. The argon is thermostatted by allowing the gas to flow through a spiral-wound copper tube outside the outer calorimeter vessel.

The temperature of the calorimeter is observed by means of the thermistor forming one of the arms in a conventional d.c. bridge circuit. A Sullivan spot galvanometer (T 2001/D) with sensitivity 0·005 μA/mm was used as a zero-point instrument. The sensitivity corresponds to a temperature change of 0·0002°C, equivalent to a change in energy of 0·002 cal.

PROCEDURE

The calorimeter was charged with *ca.* 200 mg of the substance studied and weighed to the nearest 0·01 mg. In dealing with substances exerting high vapour pressures a small evaporation was observed. However, this was shown to be reasonably constant and was not affected by temperature variations of 1°C. The calorimeter was placed in the thermostat and the temperature of the calorimeter was adjusted to that of the thermostat. The system was then allowed to equilibrate for *ca.* 15 min before the vaporization was started. The gas flow (*ca.* 15 ml/min) was adjusted and kept constant by a reducing valve and capillary tubes.

The heat loss was compensated by an intermittent addition of electrical energy in such a way that the net heat exchange with the surroundings was kept as close to zero as possible. The current was taken from a storage battery (6 V, 133 Ah) and was passed through a dummy heater of the same resistance as the calorimeter heater for about half an hour before each run. The amount of electrical energy supplied was calculated from values of the resistance of the heater, the current and the time. The current was determined by measuring the potential drop over a standard resistance in series with the heater.

The gas flow was cut off when, at most, 75 per cent of the substance had been vaporized, thus ensuring that no heat effects due to differences in adsorption were present. The amount of substance vaporized was determined by re-weighing the calorimeter. Small corrections (1 per cent or less) were applied for the amount of substance lost by evaporation during the fore and after periods of the experiment.

Note added in proof

The calorimeter described here has been further developed and is reported in *Acta Chem. Scand.* **14**, 566 (1960).

VOL. 2 1961

ÉTUDE MICROCALORIMÉTRIQUE DE LA CHALEUR D'ÉNOLISATION DE β-DICÉTONES

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Les recherches concernant la transformation cétone–énol ont été entreprises en 1910–1912 par K. Meyer[1], qui a déterminé les constantes d'équilibre cétone–énol d'un grand nombre de cétones à l'état pur et dans divers solvants. Meyer, et plus récemment Briegleb et Strohmeier[2] et Powling et, Bernstein[3] ont obtenu les chaleurs d'énolisation d'après le coëfficient de température de la constante d'énolisation. S. Sunner[4] a mesuré au calorimètre les chaleurs d'hydrolyse de l'acétate de *m*-crésyle et de l'acétate d'isopropényle et en a déduit la chaleur d'énolisation de l'acétone. Il a ainsi obtenu 7,0 kcal/mole.

On peut calculer la chaleur d'énolisation d'après la théorie des caractéristiques thermochimiques de W. Świętosławski. En supposant une additivité parfaite de l'énergie des liaisons chimiques, on obtient 0,6 kcal/mole.

La chaleur d'énolisation n'a pas jusqu'ici été mesurée calorimétriquement. Nos mesures ont été basées sur le phènomène bien connu, que la dissolution d'une dicétone dans un solvant organique est en général accompagnée d'un déplacement d'équilibre céto-énolique, ayant pour résultat une isomérisation cétone–énol aboutissant à un nouvel état d'équilibre, caractéristique pour ce solvant. On pouvait donc prévoir que la dissolution d'une dicétone dans un solvant approprié serait suivie d'un processus thermique, qu'on pourrait étudier calorimétriquement.

PRINCIPES DE LA MÉTHODE DE MESURES

C'est la microcalorimétrie dynamique sous sa forme récemment proposée par l'un de nous (M. Łaźniewski) qui nous a semblé la mieux adaptée pour ces recherches*. Voici en abrégé les principes de cette méthode.

Le calorimètre, enclos dans une enceinte isothermique, est supposé échanger la chaleur avec l'ambiance suivant la loi de Newton

$$\frac{\mathrm{d}f(t)}{\mathrm{d}t} = -\beta f(t)$$

où $f(t)$ signifie l'écart de température entre le calorimètre et les parois isothermiques et β est une constante caractérisant les conditions de l'échange thermique. Lorsque le calorimètre est le siège d'un processus thermique,

* La microcalorimétrie dynamique a été proposée en 1934 par W. Świętosławski comme méthode de mesure de faibles effets thermiques à débit constant. Voir *Microcalorimetry*, Chap. IX, Reinhold, New York, 1946, de cet auteur.

dont la loi cinétique est donnée par une fonction $g(t)$, la vitesse de l'échange thermique peut être exprimée par l'équation différentielle

$$\frac{df(t)}{dt} = -\beta f(t) + \frac{dg(t)}{dt} \tag{1}$$

En l'intégrant on trouve la loi $g(t)$ de la réaction étudiée:

$$g(t) = f(t) + \beta \int_0^t f(t)dt + f_0 + g_0 \tag{2}$$

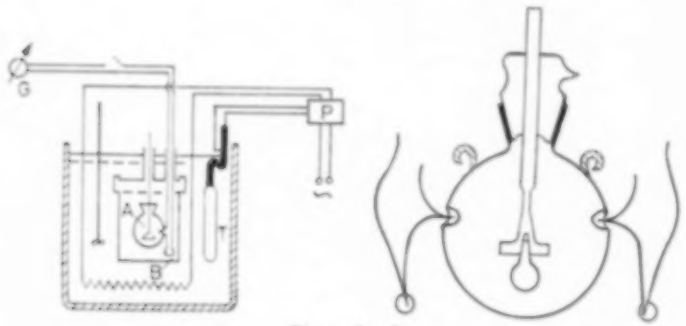
La formule obtenue admet deux constantes d'intégration: f_0 qui signifie l'écart de température entre le calorimètre et l'enceinte au moment initial $t = 0$, et g_0 qui concerne la réaction étudiée et se réduit à zéro par la nature même du problème.

La formule (2) permet de calculer la loi $g(t)$ à partir de la courbe température-temps du calorimètre et de son intégrale qu'on évalue graphiquement. La fonction $g(t)$ définit la cinétique et l'effet thermique du processus étudié.

TECHNIQUES DE MESURES

L'installation calorimétrique est montrée en schema sur la *Figure 1*.

Le calorimètre est suspendu sur des fils en nylon à l'intérieur d'un récipient B, que ferme hermétiquement un couvercle étanche vissé par des boulons. Le tout est maintenu dans un thermostat dont la température est réglée à 0,002°C. Le calorimètre en verre (*Figure 2*) est fermé par un bouchon rodé que traverse un agitateur sur baguette à rodage cylindrique.



Figures 1 et 2

Un couple thermoélectrique à quatre éléments constantan-cuivre avec un galvanomètre sensible branché dans le circuit, sert à mesurer les changements de la température du calorimètre. Le montage des thermocouples est indiqué sur la *Figure 2*. Leurs soudures paires sont fixées dans des enfonçures aux parois du calorimètre, tandis que les soudures impaires sont montées dans de petits blocs en aluminium de 2 cm de diamètre, qui pendent librement à côté du calorimètre. Ces petits blocs atteignent rapidement l'équilibre avec l'ambiance. Grâce à leur inertie thermique,

les oscillations inévitables de la température du thermostat ne s'y reflètent guère, de sorte qu'ils assurent une température de référence parfaitement fixe.

Mesures calorimétriques

Une ampoule en verre à parois fragiles contenant une dose de la dicétone étudiée est fixée à l'extrémité de l'agitateur et immergée dans le calorimètre, rempli d'une quantité connue du solvant. Le calorimètre est ensuite suspendu à l'intérieur du récipient B, lequel, le couvercle vissé, est placé dans le thermostat. Lorsque le calorimètre a atteint l'équilibre thermique avec le thermostat, on brise l'ampoule d'un coup contre le fond du calorimètre en mettant en même temps en marche l'agitateur et le chronomètre. On agite pendant une demi-minute environ pour homogénéiser le contenu du calorimètre. À partir de ce moment on enregistre systématiquement les déviations du galvanomètre.

Sur le diagramme de la *Figure* 3 nous avons reproduit, à titre d'exemple, la courbe calorimétrique $f(t)$ obtenue en mesurant la chaleur d'énolisation de l'acétylacétate ethylique.

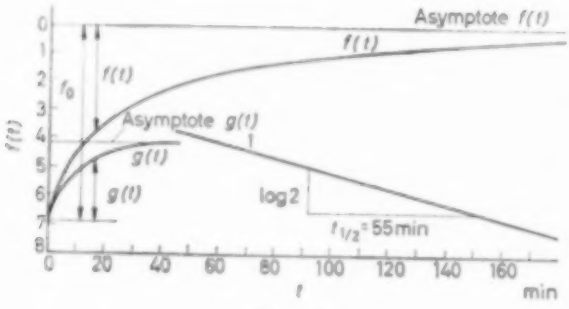


Figure 3

La dissolution de l'acétylacétate ethylique dans le benzène étant endothermique, on observe un abaissement rapide de la température du calorimètre au moment de la dissolution. Cet abaissement peut être identifié avec f_0, car la période de dissolution est négligeable auprès de la durée du processus étudié. La température du calorimètre monte progressivement par suite de la chaleur dégagée par l'énolisation et, d'autre part, à cause de l'échange thermique entre le calorimètre et les parois de B.

La chaleur dégagée par l'énolisation diminue à mesure que la solution s'approche de l'équilibre céto-énolique, et s'annule lorsque celui-ci est atteint. C'est à partir de ce moment que la courbe $f(t)$, n'étant plus perturbée par un effet thermique intrinsèque, prend le caractère exponentiel en vertu de la loi de Newton. Mise en coordonnées $\log f(t)$, temps, cette partie de la courbe se transforme en une droite dont la pente permet de déterminer, par une construction graphique bien connue, la période $t_{\frac{1}{2}}$ de la courbe. Dans l'exemple cité on a trouvé $t_{\frac{1}{2}} = 55$ min et $\beta = 0{,}693/t_{\frac{1}{2}} = 0{,}0125$ min^{-1}. On voit également sur le diagramme la courbe $g(t)$,

qu'on a obtenu d'après la formule (3). Elle représente la marche du processus étudié.

RÉSULTATS DE MESURES

Acétylacétate éthylique et benzoylacétate éthylique en solution dans le benzène

Les mesures microcalorimétriques nous ont permis d'établir que la dissolution de ces deux dicétones dans le benzène était suivie d'un effet exothermique, décroissant suivant une équation cinétique de premier ordre. Le diagramme de la *Figure 4* représente la courbe d'énolisation de l'acetylacé-

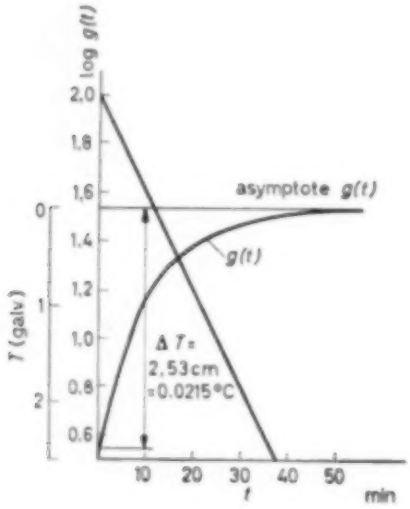


Figure 4

tate de l'éthyle. En rapportant la courbe $g(t)$ à l'asymptote et en la mettant en coordonnées semilogarithmiques on la transforme en une droite qui, extrapolée à $t = 0$, fournit la valeur totale de l'accroissement ΔT dû à l'effet thermique du processus étudié. On l'exprime en calories à l'aide de la formule usuelle $q = K\Delta T$. Nous attribuons cet effet à la chaleur d'énolisation dégagée dans la transformation cétone–énol qui a lieu en solution. Il peut être recalculé pour 1 mole de la cétone isomérisée

Tableau 1. Chaleur d'énolisation en solution benzénique

	$CH_3COCH_2COOC_2H_5$		$C_6H_5COCH_2COOC_2H_5$	
Chaleur d'énolisation Q(kcal/mole)	1,61	1,60	1,94	1,95
Temps de demi-réaction $t_{\frac{1}{2}}$(min^{-1})	15	15,5	11,6	11,0

d'après les données analytiques concernant sa teneur en énol à l'état pur et en solution. Le *Tableau 1* contient quelques données, citées à titre

VOL. 2 1961

d'exemple, d'après lesquelles la chaleur d'énolisation de l'acétylacétate ethylique est de 1,6 kcal/mole et celle de benzoylacétate 1,95 kcal/mole.

Acétylacétone en solution dans le benzène et l'ether acétylacétique en solution dans le hexane

L'étude microcalorimétrique nous a fourni, dans ces deux cas, les courbes du débit thermique qui diffèrent de celles mentionnées plus haut. Contrairement à celles-ci, elles ne se laissent pas représenter par une fonction exponentielle $g(t) = G(1 - e^{-kt})$. On peut cependant les décomposer d'une façon univoque en deux fonctions exponentielles simples, $g_1(t) = g_1^0(1 - e^{-k_1 t})$ et $g_2 = g_2^0(1 - e^{-k_2 t})$, pour lesquelles g_1^0 et g_2^0 sont les valeurs asymptotiques dont la somme est la valeur asymptotique de la fonction $g(t)$

$$g^0 = g_1^0 + g_2^0$$

La fonction $g(t)$ peut donc être mise sous la forme

$$g(t) = g_1^0(1 - e^{-k_1 t}) + g_2^0(1 - e^{-k_2 t}) \qquad (3)$$

Un exemple de la courbe globale avec ses deux composantes est représenté par le diagramme de la *Figure 5*. On voit clairement que les valeurs

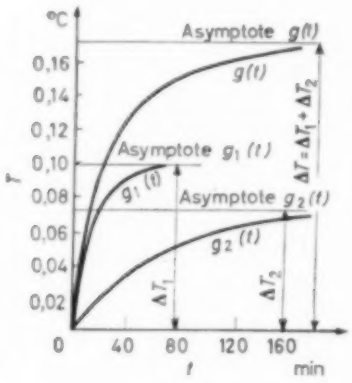


Figure 5

asymptotiques g^0, g_1^0 et g_2^0 s'identifient avec les accroissements de température ΔT, ΔT_1 et ΔT_2 lesquels remplissent la condition $\Delta T = \Delta T_1 + \Delta T_2$. Multipliés par la capacité thermique du calorimètre et recalculés pour une mole de la cétone dissoute ils donnent la totalité du débit thermique sous forme d'une somme de deux débits partiels $q = u_1 + u_2$.

Nous avons tenté l'expliquation de ces résultats en supposant que dans le cas considéré l'énolisation d'une β-dicétone était suivie d'un réarrangement intramoléculaire de l'énol avec formation de structures chelatées.

La courbe globale de l'effet thermique résulterait alors de deux processus monomoléculaires consecutifs suivant le schema

$$\text{cétone} \xrightarrow{k_1} \text{énol} \xrightarrow{k_2} \text{structure chelatée}$$

où k_1 et k_2 signifient les deux constantes de vitesse.

Considérons, pour fixer les idées, une mole d'une β-dicétone dans un solvant énolisant. Appelons N_1^0 la quantité de la forme cétonique qui s'énolyse sous l'action du solvant et N_2^0 la quantité de la forme énolique présente dans le composé pur. D'après la théorie des réactions monomoléculaires consécutives on peut immédiatement écrire la formule d'énolisation en fonction du temps

$$N_2(t) = N_1^0(1 - e^{-k_1 t}) \tag{4}$$

et la formule d'accumulation de la forme chelatée

$$N(t) = N_2^0(1 - e^{-k_2 t}) + N_1^0\left[\frac{k_2}{k_2 - k_1}(1 - e^{-k_1 t}) - \frac{k_1}{k_2 - k_1}(1 - e^{-k_2 t})\right] \tag{5}$$

En introduisant la notion de la chaleur moléculaire d'énolisation, Q_1, et de la chaleur moléculaire de chelation, Q_2, on trouve le débit thermique d'énolisation

$$q_1(t) = Q_1 N_1^0(1 - e^{-k_1 t}) \tag{6}$$

et celui de la chelation

$$q_2(t) = Q_2 N_2^0(1 - e^{-k_2 t}) + Q_2 N_1^0\left[\frac{k_2}{k_2 - k_1}(1 - e^{-k_1 t}) - \frac{k_1}{k_2 - k_1}(1 - e^{-k_2 t})\right] \tag{7}$$

l'un et l'autre en fonction du temps.

La chaleur dégagée au cours du processus étudié est la somme de ces deux effets. Après réarrangement, la courbe du débit thermique est facilement mise sous la forme

$$q(t) = \left(Q_1 N_1^0 + \frac{k_2}{k_2 - k_1} Q_2 N_1^0\right)(1 - e^{-k_1 t}) + \left(Q_2 N_2^0 - \frac{k_1}{k_2 - k_1} Q_2 N_1^0\right)(1 - e^{-k_2 t}) \tag{8}$$

qui est la somme de deux fonctions exponentielles du temps.

Ce résultat nous permet d'interpréter les quantités U_1 et U_2 qu'on peut visiblement identifier avec les valeurs asymptotiques de fonctions composantes (3). On a alors

$$U_1 = Q_1 N_1^0 + \frac{k_2}{k_2 - k_1} Q_2 N_1^0 \qquad U_2 = Q_2 N_2^0 - \frac{k_1}{k_2 - k_1} Q_2 N_1^0 \tag{9}$$

ce qui permet de calculer les chaleurs moléculaires d'énolisation, Q_1 et de chelation, Q_2 d'après les formules

$$Q_1 = \frac{U_1}{N_1^0} - \frac{k_2}{k_2 - k_1} Q_2 \qquad Q_2 = \frac{U_2}{N_2^0 - \frac{k_1}{k_2 - k_1} N_1^0} \tag{10}$$

VOL. 2 1961

Quelques résultats de tels calculs se trouvent dans le *Tableau 2.*

Tableau 2. Chaleurs d'énolisation et de chelation

	$CH_3COCH_2COCH_3$ (*solvant* C_6H_6)		$CH_3COCH_2COOC_2H_5$* (*solvant* C_6H_{14})	
	$N_1^0 = 0{,}089$	$N_2^0 = 0{,}762$	$N_1^0 = 0{,}427$	$N_2^0 = 0{,}073$
Solvant (g)	461,0	437,5	323,0	325,0
Cétone (g)	3,6242	5,1482	1,7004	2,6791
ΔT_1 (°C)	0,0387	0,0576	0,0590	0,0931
ΔT_2 (°C)	0,0063	0,0135	0,0510	0,0676
u_1 (cal/mole)	232	232	913,0	916,8
u_2 (cal/mole)	38	55	785,0	665,8
k_1 (min^{-1})	0,231	0,198	0,0693	0,0630
k_2 (min^{-1})	0,051	0,080	0,0147	0,0126
Q_1 (kcal/mole)	2,63	2,65	2,48	2,42
Q_2 (kcal/mole)	0,04	0,06	1,28	1,10

* D'après les données de Powling et Bernstein la chaleur d'énolisation de l'acétylacétate dans le hexane est de 1,60 kcal/mole.

Les formules (10) tiennent compte de l'équilibre céto-énolique en solution par la definition même de N_1^0, tandis que faute de données nécéssaires elles supposent que l'énol est entièrement converti en chelat.

L'ether acetylacétique en solution alcoolique

En étudiant au microcalorimètre la dissolution de l'ether acétylacétique dans l'alcool absolu, nous avons constaté un dégagement de chaleur à débit de 575 cal/mole de la cétone, qui décroît suivant une loi exponentielle. Attribué à l'énolisation cet effet donnerait 16,9 kcal/mole comme chaleur d'énolisation—un résultat visiblement inadmissible. C'est pourquoi nous avons supposé que l'effet observé était de nature complexe, analogue à celui qu'on observe en solutions d'acétylacétone dans le benzène et de l'ether acétylacétique dans le hexane. La forme apparement unimoléculaire de la courbe thermique pouvait s'expliquer en supposant, qu'en solution alcoolique les deux processus avaient à peu près la même vitesse. Pour vérifier cette hypothèse nous avons repris nos experiences dans un solvant non énolisant. (Suivant nos mesures, un tel solvant est fourni par un mélange alcool–eau à 87 sur cent d'alcool.) Malgré l'élimination de l'énolisation nous avons trouvé un débit thermique de 506 cal/mole de l'ether dissout. La difference, 69 cal/mole recalculée pour 1 mole de la cétone énolisée, donne 2,03 kcal/mole comme chaleur d'énolisation.

L'effet thermique observé dans le solvant non énolisant peut servir à calculer l'énergie de la chelation si l'on suppose qu'en solution alcoolique la forme énolique de l'ether acetylacétique se convertit entièrement en chelat. D'après la teneur de l'acétylacétate en énol, on trouve 6,9 kcal/mole. Tout récemment H. Feilchenfeld[5] a cité 6,0 kcal comme valeur généralement admise pour l'énergie de la liaison d'hydrogène.

Considérons encore l'effet thermique que nous désignons comme chaleur de chelation. Pour l'ether acétylacétique en solution alcoolique il atteint 6,9 kcal/mole. Il se réduit à 1,2 kcal dans le hexane et est pratiquement nul dans le benzène. Le même effet en solution benzènique de l'acétylacétone est à peine de 0,05 kcal. Ces faits témoignent d'une complexité

marquée de ce phènomène, qui probablement est dû à l'influence du milieu et dont l'interpretation reste encore incertaine dans bien des points.

Toutefois les données obtenues dans des conditions d'expériences différentes témoignent en faveur de l'hypothèse de deux processus consécutifs.

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VOL
2
1961

FLUORINE BOMB CALORIMETRY*

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INTRODUCTION

There are many inorganic compounds for which heat of formation values have not been measured, often because of the lack of suitable experimental methods. Exploratory experiments in this laboratory in oxygen bomb and aqueous solution calorimetry on various transition metal borides, sulphides and silicides re-emphasized the need for a general method for determining the heat of formation of compounds not amenable to conventional thermochemical calorimetry. With the aim of developing such a method, attention was directed towards the use of fluorine as an oxidant in calorimetry.

The use of fluorine in calorimetry is not a new idea. However, in previous work it was used when necessary in the investigation of the heat of a particular reaction, rather than as a general tool.

As early as 1926, Wartenberg and his co-workers used fluorine flow calorimetry in some of their studies, synthesizing HF [1], F_2O [2] and AgF_2 [3] in a calorimeter. Wartenberg[4] has also treated silicon, carbon and silicon carbide and more recently, at the National Bureau of Standards, Jessup and Armstrong[5–7] have treated CoF_2 [5], CH_4 [6] and NH_3 [7] with fluorine in a flow-type calorimeter. P. Gross[8] has treated titanium and sulphur with fluorine in a constant volume glass vessel in a calorimeter. Various fluorine-containing compounds have also been made to react with other compounds in a calorimeter, *e.g.*, NF_3 with H_2 [9], CrF_3 with Mg [10], CrF_4 with H_2 [10], CoF_2 with KOH [11], CoF_3 with $C_6H_4(CF_3)_2$ and H_2 [5], K with CF_4 [12] and ClF_3 with NaCl.

In solution calorimetry the use of aqueous hydrofluoric acid as the solvent is well documented. The use of BrF_3 as a non-aqueous solvent in solution calorimetry has been suggested by Woolf[14–16]. Woolf[16] also suggested the possibility of fluorine bomb calorimetry, but expressed a preference for BrF_3 solution calorimetry.

It was decided in this laboratory to develop fluorine bomb calorimetry as a general tool for studying compounds not easily studied with conventional calorimetric methods. Information on the chemistry of bromine trifluoride and fluorine reactions indicates that the reactions in fluorine bomb calorimetry appear to be more easily characterized and adapted to calorimetric study than the reactions in bromine trifluoride solution calorimetry.

* Work performed under the auspices of the U.S. Atomic Energy Commission.

CONSTRUCTION MATERIALS AND SAFETY FEATURES

Although fluorine is recognized as a very dangerous material, it can be handled without undue hazards if proper materials of construction are used and reasonable safety precautions are taken.

Nickel and Monel are by far the best general-purpose materials to use in the construction of apparatus for handling fluorine. However, where use of nickel and Monel is not possible, copper, brass, stainless steel or aluminium may be substituted. For gaskets, aluminium, tin, copper or lead may be used. For valve packing or gasketting, poly(tetrafluoroethylene) (Teflon) may be used, if well protected.

Lines and components permanently joined should be welded. Silver solder may be used on temporary apparatus or where its use is unavoidable. For permanent joints, where welding is impossible, threaded or flanged pipe fittings should be used. For frequently disconnected joints standard flare- or ferrule-type tubing fittings may be used.

Various commercially available valves have been tried in the fluorine bomb calorimetric work and found to be satisfactory. All of them had Monel bodies and nickel stems. For higher pressures valves packed with poly(tetrafluoroethylene) were employed. For lower pressures (up to 5000 mm) a diaphragm type of valve was used in which the diaphragm was sealed with an aluminium gasket. Another type of valve used where weight or space was limited and brass and silver solder could be tolerated was a small packless Monel valve with a nickel stem and brass bellows. The bomb valves were specially made. These valves, except for the K-Monel stems, were made mostly of nickel and were packed with a washer of poly(tetrafluoroethylene).

The pressure gauges used were all Bourdon tube gauges with welded Monel tubes.

The resistance of nickel and the other metals of construction to fluorine depends upon the formation of a protective fluoride film. Before any equipment, lines or components were put into service they were thoroughly cleansed of all foreign matter and prefluorinated cautiously until conditions were reached under which the system was to be operated. Prefluorination of the interior surfaces of the bomb was carried out under increasingly severe conditions until the bomb containing fluorine was held at 200°C for ten hours. A very adherent and coherent protective film of nickel fluoride was thus produced, sufficient to prevent significant further reaction of the nickel with fluorine.

An important precaution which has become standard practice in our laboratory is to expose the prefluorinated bomb only to dry atmospheres. This is done by handling the open bomb only in a dry box. In this way adsorption of moisture by the bomb or its contents is avoided.

The following safety precautions were used during bomb charging and discharging operations. Valves were operated by manually activated extensions passing through a 0·25 in. plastic or safety glass barricade. The entire apparatus was enclosed in a well-ventilated hood. The high pressure fluorine supply tank and bomb charging system were enclosed in 0·25 in. steel plate. To facilitate smoother and less hazardous reduction of pressure double valves and a ballast tank were employed.

While manipulating the equipment the operator always wore a leather coat, leather gloves and a face shield.

After the bomb is placed in the calorimeter a hazard may arise from possible leakage of fluorine into the surrounding water bath. Experiments were carried out with deliberate leaks of up to 500 cm^3/min through a small hole, which showed that the reaction occurred without sufficient violence to present a hazard to the operator.

THE BOMB AND FLUORINE HANDLING APPARATUS

The bomb used for the calorimetric experiments is dimensionally identical with the bombs used in this laboratory for oxygen bomb calorimetry[17]. The body and cap of the bomb are fabricated of pure nickel and are sealed with a 0·06 in.-thick soft aluminium gasket. The valve housings of the bomb are made of nickel and screwed into the bomb cap, the seal being effected with a lead gasket. The stem of the valve is made of K-Monel and sealed with a washer of poly(tetrafluoroethylene).

To contain the sample in the bomb before and during the combustion reaction is one of the more formidable problems of fluorine bomb calorimetry. Various arrangements of sample supports and electrodes within the bomb have been employed.

The samples to be studied can be classified according to the type of container or support that is required as follows:

(1) those that do not undergo significant spontaneous reaction with fluorine and can be fabricated into a shape that can be suspended in the bomb;
(2) those that do not undergo significant spontaneous reaction but require a support such as a crucible;
(3) those that react spontaneously with fluorine and require isolation from the fluorine before the main period.

The easiest substances to handle are those of the first class, in which the sample is in the form of a wire or sheet suspended in the bomb. For combustions of molybdenum, an example of this type, the sample was 0·005 in. thick sheet and was suspended from an insulated rod by a short length of molybdenum wire 0·005 in. in diameter. Two nickel electrodes were also provided between which was attached a molybdenum ignition wire which had been threaded through holes at the bottom of the sample. Other experiments were carried out in which the sample was in the form of a suspended coiled wire.

Samples of the second class require a crucible or disc support. For these samples the most promising technique that has been tried is a nickel crucible lined with a stable fluoride, preferably the fluoride of the metal involved in the reaction. Nickel crucibles are attacked in combustions of many substances, but may be useful for a limited number of reactions.

Samples of the third class require isolation of the sample from fluorine before intentional ignition. One technique for this, on which some experimentation has been done, is the enclosing of the sample in a thin weighed metal foil of cadmium, indium, lead, tin or zinc. The foil is sealed by either welding or crimping. Another possible technique is the

use of quartz ampoules in much the same way as they are used for various organic compounds.

With whatever sample support method is used, ignition of the sample is accomplished by the passage of an electric current through an ignition wire close to or touching the sample. When metal fluorinations are being studied the same metal is generally used for the ignition wire. Because of the reactivity of fluorine most ignition wires, regardless of the metal used, will ignite and break the circuit. Consequently, a current integrating device, similar to that described by Pilcher and Sutton[18], is used to measure the ignition energy.

The bomb charging equipment consists of a fluorine supply tank, a sodium fluoride trap to remove traces of hydrogen fluoride, a ballast tank, and appropriate valves, gauges, and lines with connections to the bomb, an inert gas supply and a vacuum system. The sodium fluoride trap is easily regenerated by heating *in situ* at 250–300°C while purging with dry nitrogen.

The bomb discharging equipment consists of a series of cold traps with appropriate connections to the bomb, a Booth–Cromer pressure gauge[19], an infra-red spectrum cell, an inert-gas supply, and the vacuum system. The vacuum pump is protected from fluorine by a large, dry soda-lime trap. The cold traps are provided to permit trap-to-trap distillation of the product gases to aid in their identification by vapour pressure measurements or by spectral analysis. The infra-red cells were made of nickel with windows of barium fluoride, calcium fluoride, silver chloride, or polyethylene.

VOL
2
1961

THE CALORIMETER AND ITS CALIBRATION

A bomb calorimetric system similar to that described by Hubbard, Katz and Waddington[17] was employed, the calorimetric observations being taken in the usual manner. The calibration of the system was carried out by combustions of benzoic acid in the bomb according to standard practice. However, since the electrodes, sample supports and other internal fixtures are different in the calibration and combustion experiments, the " contents of the bomb " for which heat capacity corrections are made include all such internal components.

Fluorine

Three grades of fluorine have been used in our work:

(1) a high-purity (99–99·5 per cent) commercial grade, no longer available;

(2) commercially available fluorine of modest purity (97·5–98·5 per cent); and

(3) fluorine fractionated at liquid nitrogen temperatures, of which the best fraction has an impurity content of less than 0·1 per cent.

EXPERIMENTAL PROCEDURE

The experimental procedure used in carrying out an experiment in fluorine bomb calorimetry involves very little that has not been either inferred or discussed previously. After the sample is placed in the bomb in one of the various sample-support arrangements, the bomb is closed,

connected to the charging apparatus and evacuated. Fluorine from the storage tank is allowed to enter the ballast tank until a pressure somewhat greater than the desired charging pressure is reached. The valves to the storage tank are then closed, the bomb charged to pressure, the connecting lines are broken, and the bomb is placed in the calorimeter where the calorimetric measurements are carried out in the usual manner.

After the experiment the bomb is connected to the discharging apparatus and, from this point on, the procedure varies with the particular reaction carried out and the analytical tests necessary. For gaseous reaction products tests are carried out in the apparatus previously discussed. For solid reaction products the usual identification by X-ray diffraction techniques and chemical analyses may be carried out on the bomb residue.

The standard state corrections are made according to the procedure of Hubbard, Scott and Waddington[20]. However, the calculations are far less complicated for combustions in fluorine since no water is added to the bomb. The equation of state[21], $PV = RT - 0{\cdot}0196\,P$ l. atm., applies to fluorine gas; $(\partial E/\partial P)_T$ for fluorine at 25°C is $-1{\cdot}78$ cal mole^{-1} atm^{-1}.

CONCLUSION

The fluorine bomb calorimetric techniques which have been presented in this paper were developed from many exploratory experiments with approximately 25 metallic or metalloid elements and 15 inorganic compounds representing their combinations. The reactions of three-quarters of these substances with fluorine immediately appeared to be suitable for calorimetric study, being rapid, complete, and well defined. With the remaining substances the reactions, under the conditions used in these brief explorations, were not self-sustaining or led to a mixture of products.

Although fluorine bomb calorimetry is still in its infancy and many of the techniques used have yet to stand the test of time, it can be concluded with confidence that (1) fluorine bomb calorimetry can be carried out without undue hazard to the investigator; (2) suitable materials of construction can be found for the bomb and auxiliary apparatus, and (3) fluorine bomb calorimetry will be very useful in the determination of heats of formation of many fluorides, practically the entire measured energy being due to the heat of formation of the compound.

It is quite apparent that the formation of fluorides by the fluorine bomb combustion of many elements and inorganic compounds will rapidly become a useful tool for thermochemical studies of modern calorimetric precision.

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VOL.
2
1961

COMBUSTION CALORIMETRY OF ORGANIC BROMINE COMPOUNDS: THE ACCURACY OF DATA OBTAINED WITH A MOVING-BOMB TECHNIQUE

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A moving-bomb calorimetric method for measuring heats of combustion at 25°C of solid and liquid organic bromine compounds has recently been developed[1]. The calorimetric system is calibrated by combustion of standard benzoic acid under certified bomb-calibrating conditions. In order to obtain well-defined equilibrium final states in the bomb in combustion experiments with bromine compounds, however, the bomb liquid must differ both in nature and amount from that specified for calibration experiments with benzoic acid. Thus, 3 g of water per litre of bomb volume are used in the calibration experiments, whereas 112 g of 0·06 M arsenious oxide solution per litre of bomb volume are used in the combustion experiments with bromine compounds. Calibration experiments with benzoic acid and combustion experiments, with paraffin oil and with *p*-bromobenzoic acid have all given results of a precision slightly better than 0·01 per cent. This demonstrates that the various additional complications introduced into the procedure by the presence of a reasonable percentage of bromine in the sample do not affect the precision obtainable with the given apparatus and procedure. Although the precision of the method has thus been found to be satisfactorily high, the difference in conditions of combustion and calibration experiments may give rise to non-cancelling systematic errors. Therefore the accuracy of the heat of combustion data obtained has to be investigated. Since the principal use for heat of combustion data is to derive corresponding heats of formation, a suitable approach would be to compare, for certain selected bromine compounds, heats of formation calculated both from heat of combustion data and from calorimetric data on heats of reactions other than combustion. Such a comparison has been made and the results will be briefly reported here.

HEAT OF COMBUSTION DATA

Samples of the compounds listed in *Table 1* were carefully purified. The products obtained were found to have the density and refractive indices given in the same table. From heat of combustion experiments with the pure samples the standard heats of combustion at 25°C given in *Table 2* were obtained. In the same table are also listed heat of vaporization data calculated from published information[2–4].

Table 1. Density and refractive indices for the samples used in the heat of combustion experiments

Compound	d (g/ml)		n_D	
	20°C	25°C	20°C	25°C
1,2-Dibromobutane	1·7954	1·7870	1·5149	1·5125
1,2-Dibromocyclohexane	1·7903	1·7833	1·5529	1·5506
1-Bromopropane	1·3550	1·3465	1·4346	1·4320
2-Bromopropane	1·3142	1·3055	1·4255	1·4226
2-Bromobutane	1·2607	1·2533	1·4370	1·4345

Table 2. The heats of combustion and vaporization at 25°C

Compound (*liq.*)	$-\Delta H_c^\circ$ (kcal/mole)*	ΔH_v (kcal/mole)†
1,2-Dibromobutane	614·15 ± 0·54	10·80 ± 0·20
1,2-Dibromocyclohexane	867·45 ± 0·60	
1-Bromopropane	491·50 ± 0·34	7·75 ± 0·20
2-Bromopropane	490·37 ± 0·42	7·30 ± 0·20
2-Bromobutane	646·50 ± 0·30	8·45 ± 0·25

* The uncertainties given in this column are equal to twice the final " over-all " standard deviation.
† The values given in this column refer to the process $C_nH_nBr_{d(L)} \longrightarrow C_nH_nBr_{d(g.)}$, at saturation pressure at 25°C. The uncertainties given are estimated.

VOL. 2 1961

COMPARISON OF HEAT OF FORMATION DATA FROM DIFFERENT METHODS

The standard heats of formation calculated from the heat of combustion data of *Table 2* are compared in *Table 3* with heats of formation calculated from heat of reaction data for the following reactions: addition of bromine to but-1-ene[5,6] and to cyclohexene[6]; addition of hydrogen bromide to

Table 3. Comparison of heats of formation from several methods

Substance	*Standard heat of formation at* 25°C (kcal/mole)		
	From heat of combustion data	*From other heat of reaction data*	*Difference*
1,2-Dibromobutane (g)	− 24·54 ± 0·58	− 22·47 ± 0·44[a]	− 2·07 ± 0·70
		− 21·58 ± 0·63[b]	− 2·96 ± 0·78[b]
1,2-Dibromocyclohexane (liq.)	− 38·46 ± 0·60	− 40·15 ± 0·46[c]	+ 1·69 ± 0·76
1-Bromopropane (g)	− 22·02 ± 0·40	− 21·77 ± 0·34[d]	− 0·25 ± 0·52
		− 21·13 ± 0·40[e]	− 0·89 ± 0·57
2-Bromopropane (g)	− 23·60 ± 0·46	− 24·07 ± 0·24[f]	+ 0·47 ± 0·52
2-Bromobutane (g)	− 28·69 ± 0·40	− 28·55 ± 0·30[g]	− 0·14 ± 0·50

[a] From[5]: but-1-ene (g) + bromine (g) ⟶ 1,2-dibromobutane (g).
[b] From[6]: but-1-ene (in CCl_4) + bromine (liq.) ⟶ 1,2-dibromobutane (in CCl_4).
[c] From[6]: cyclohexene (in CCl_4) + bromine (liq.) ⟶ 1,2-dibromocyclohexane (in CCl_4).
[d] From[7]: cyclopropane (g) + hydrogen bromide (g) ⟶ 1-bromopropane (g).
[e] From[10]: 1-bromopropane (g) + hydrogen (g) ⟶ propane (g) + hydrogen bromide (g).
[f] From[5,8]: propene (g) + hydrogen bromide (g) ⟶ 2-bromopropane (g).
[g] From[8]: butene (g) + hydrogen bromide (g) ⟶ 2-bromobutane (g). The value given is the mean of the three values calculated from the heats of hydrobromination of the three different normal butenes.
[h] This uncertainty is lower than the combined uncertainties of the two heats of formation given in the preceding columns since the uncertainty in the heat of vaporization of 1,2-dibromobutane cancels in the difference.

cyclopropane[7], propene[7,8], but-1-ene[9], *cis*-but-2-ene[9], and *trans*-but-2-ene[9], respectively; hydrogenation of 1-bromopropane to propane[10].

It is seen from *Table 3* that for 1,2-dibromobutane and 1,2-dibromocyclohexane the differences in the heats of formation obtained from different methods are significantly greater than the estimated uncertainties of the differences. It is to be noted that for the two comparisons with results from the work of Lister, the differences obtained are of opposite sign.

The accord of the heats of formation calculated from heat of combustion data with the heats of formation calculated from heats of reaction given by Lacher and co-workers is very good.

Note added in proof

A full account of this work will be presented in: L. Bjellerup. *Acta Chem. Scand.*, **15** (1961), in press.

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VOL.
2
1961

THE HEAT OF DISSOCIATION OF NITROGEN

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The heat of dissociation of nitrogen has been studied many times and the latest values are shown in *Table 1*. The three experimental methods give somewhat discordant results. By methods I, II and IV, $D(N_2) = 9{\cdot}765$ eV.* Method I does not eliminate $D(N_2) = 7{\cdot}373$ eV. $D(N_2) = 11{\cdot}8$ eV by methods III and IV. $D(CN) = 8{\cdot}2$ and $8{\cdot}5$ eV respectively by methods II and III, while method IV gives a lower result. It is evident that $D(N_2) = 9{\cdot}765$ eV is the most likely value[1–6].

However, a higher value $D(N_2) = 11{\cdot}8$ eV, was suggested on the basis of the following comparisons. The internuclear distance (R_0) and the force constants (k_e) of the structures MH_x(M = C, N, O, F; x = 1 to 4) were plotted against the number of H atoms, giving plots of great regularity (*Figure 1*, *Table 3*). The basic sequence is C, N, O, F. It should be noted

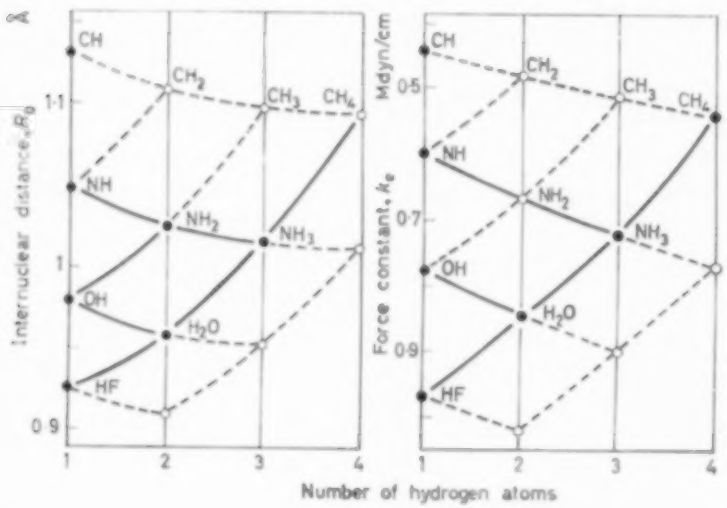

Figure 1

that every point must lie on two crossing curves and on the vertical lines of a given number of hydrogen atoms, in order to produce these networks. It was expected that bond energies would behave similarly (*Figure 2*). However, with[7] $L(C) = 170{\cdot}4$ kcal and the likely $D(N_2) = 9{\cdot}765$ kcal, the sequence is N, C, O, F. This change seemed rather unexpected since bond energies are known to behave in a regular manner with internuclear

* Symbols are defined at the end of the paper.

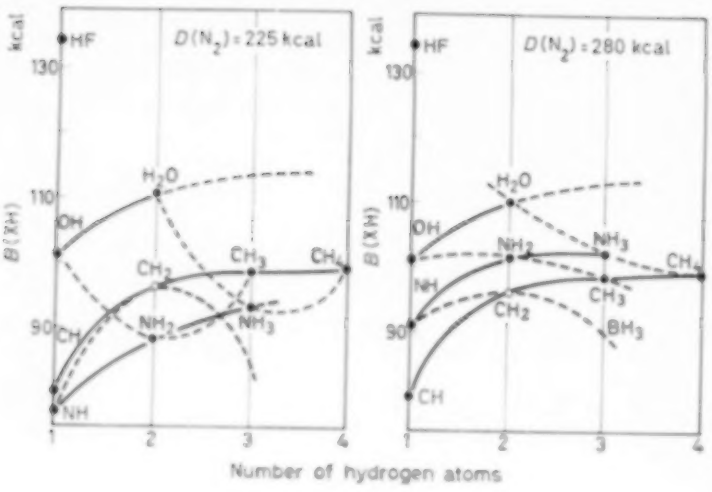

Figure 2

Table 1. Heat of dissociation of nitrogen

Method	*D*(N_2) (eV)		*D*(CN) (eV)	*Ref.*
I. Spectroscopy	9·765	7·373	—	1
II. Qf(CN); $\bar{T}$(CN)	9·765	—	8·2	2, 3
III. N_2/CO terms	—	11·8	8·5	4
IV. Shock-wave	9·765	11·8	7·6	5
»	9·765	—	—	6

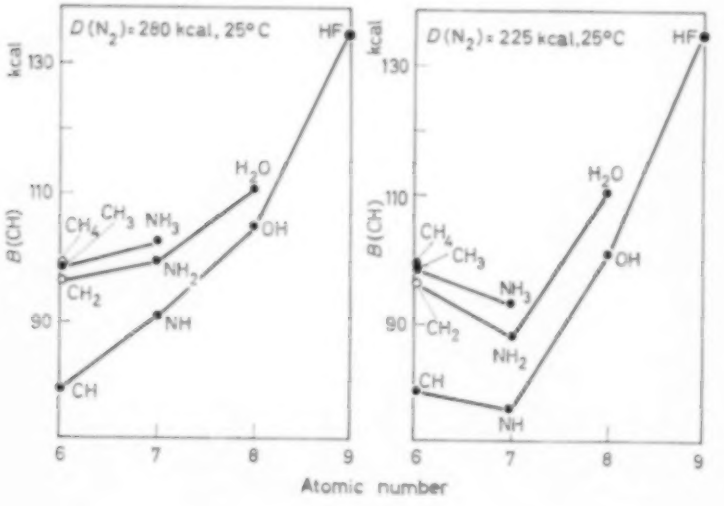

Figure 3

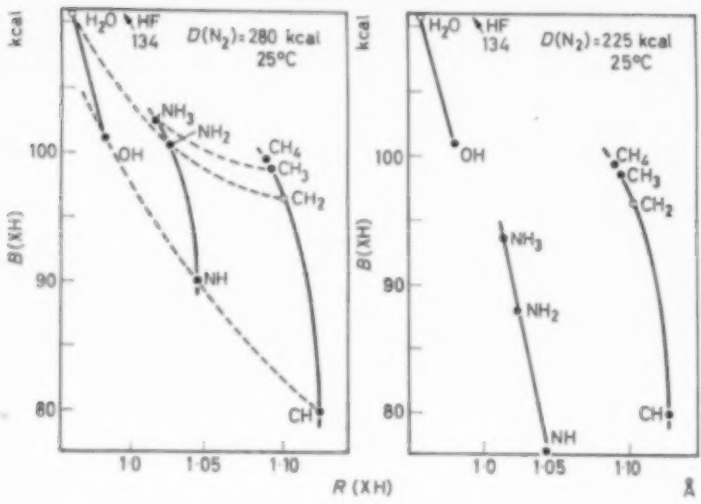

Figure 4

distances. An increase in $D(N_2)$ would raise all $B(NH)$ values. $D(N_2) = 11{\cdot}8$ eV was suggested because the term values of N_2 and CO stand in the ratio[4] 1 : 1·066. Another possible value is $D(N_2) = 12{\cdot}14$ eV since a pre-dissociation exists in the nitrogen energy level system at 97944 cm^{-1}. If this level is connected with the dissocation process, then lower levels must be perturbations. A lower value ($D(N_2) = 265$ kcal) was also studied, since then the NH curve would still lie above the CH curve. The comparison of these $D(N_2)$ values is shown in *Table 2*.

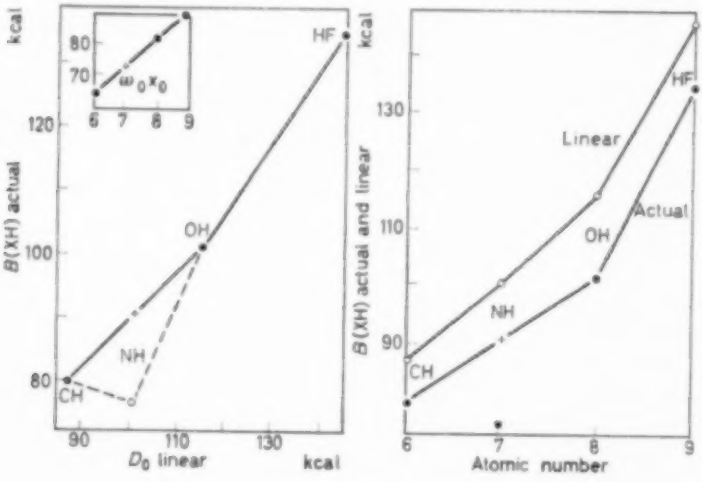

Figure 5

Table 2. Comparison of $D(N_2)$ values

Reference	(2, 3)	(5)	(6)	(4)
$D(N_2)$ (kcal)	225·0	225·0	265·0	280·0
D(NC—CN) (kcal)	114·0	141·5	141·5	141·5
$2C_{(gr)} + N_{2(g)} \rightarrow C_2N_{2(g)}$	− 73·6	− 73·6	− 73·6	− 73·6
$2C \rightarrow 2C_{(gr)}$	340·7	340·7	340·7	340·7
$2N \rightarrow N_{2(g)}$	225·0	225·0	265·0	280·0
$2C + 2N \rightarrow C_2N_{2(g)}$	492·1	492·1	532·1	547·1
$C_2N_{2(g)} \rightarrow 2CN$	−114·4	−141·5	−141·5	−141·5
$2C + 2N \rightarrow 2CN$	377·7	350·6	390·6	405·6
$C + N \rightarrow CN$	188·8	175·3	195·3	202·8
$N_{2(g)} \rightarrow 2N$	−225·0	−225·0	−265·0	−280·0
$2C_{(gr)} \rightarrow 2C$	−340·7	−340·7	−340·7	−340·7
$2C + 2N \rightarrow 2CN$	+377·7	+350·6	+390·6	+405·6
$2C_{(gr)} + N_2 \rightarrow 2CN$	−188·0	−215·1	−215·1	−215·1
$C_{(gr)} + \frac{1}{2}N_{2(gr)} \rightarrow CN$	−94·0	−107·6	−107·6	−107·6

Table 3. Bond energies, distances and force constants of $(MH)_X$; M = C, N, O, F; X = 1, 2, 3, 4. L(C) = 171·7; $D(H_2)$ = 104·2; $D(O_2)$ = 118·3; $D(F_2)$ = 37·6; $D(N_2)$ = 225 or 280 kcal

	R(CH) (A°)	B(CH) (kcal)	Q_a (kcal)	D (kcal)	$10^6 k_e$ (Mdyn/cm)
CH_4	1·093	99·5	398·0		0·539
				101·6	
CH_3	(1·096)	98·8	296·4		(0·470)
				(103·4)	
CH_2	(1·108)	(96·5)	(193·0)		(0·450)
				(113·0)	
CH	1·13	80·0	80·0		0·448
				80·0	
				398·0	
NH_3	1·016	99·9	299·7		0·717
				104·0	
NH_2	1·023	97·9	195·7		0·615
				105·7	
NH	1·048	90·0	90·0		0·600
				90·0	
($D(N_2)$ = 265 kcal)				299·7	
NH_3	1·106	93·5	280·5		0·717
				104·1	
NH_2	1·025	88·2	176·4		0·615
				99·4	
NH	1·048	77·0	77·0		0·600
				77·0	
($D(N_2)$ = 225 kcal)				280·5	
H_2O	0·957	110·6	221·2		0·843
				120·0	
OH	0·980	101·2	101·2		0·779
				101·2	
				221·2	
HF	0·926	135·0	135·0	135·0	0·966

VOL. 2 1961

From appearance potentials D(NC—CN) = 6·9 eV uncorrected for the kinetic energy of the products[8]. The correction[9] is 0·57 eV and gives D(NC—CN) = 6·3 eV or 145 kcal, in good agreement with the results of shock-tube experiments (141·5 kcal).

Electron-impact experiments[10, 11] show that N^+ ions appear at 24·3 eV, leading to $D(N_2)$ = 225 kcal. In the past such experiments on CO yielded D(CO) = 9·6 eV. However, the latest value is 11·1 eV. A similar change in $D(N_2)$ would bring the higher value suggested here within the range of possibilities.

The relationships shown in *Figure 2* are shown in a different manner in *Figures 3–5*. It seems that any method that might elucidate this problem of hydride energies should be tried since theoretical calcuations are of extreme difficulty[12]. The only suggestion made here is that the value accepted at present will only stand if the supposed anomaly in the sequence of B(MH) values is accounted for.

Notation

B(AB, ABC) = bond energy of the bond AB in the molecule or radical ABC
D(AB) = bond energy or bond dissociation energy in the diatomic molecule or radical AB
D(AB—CD) = bond dissociation energy of ABCD into AB and CD
k_e = force constant (Mdyn/cm)
L(C) = heat of sublimation of graphite at 0°K = 170·4 kcal
R_e = effective internuclear distance

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VOL
2
1961

HEAT OF FORMATION OF CO-ORDINATION COMPLEXES OF BORON, ALUMINIUM AND GALLIUM

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One of the prerequisites to a full understanding of the nature of co-ordination compounds is a knowledge of the strength of the donor–acceptor bonds which hold them together. In many complexes the situation is complicated by the presence of several such bonds; for example the compound may be 4-, or 6-co-ordinate so that several terms go to make up the total heat of formation of the complex. For this reason it was decided to study simple 1 : 1 and 1 : 2 addition compounds rather than the usual octahedral, square, or tetrahedral complexes. In this way we hoped to be able to interpret the various energy terms more satisfactorily and so arrive at a sequence of strengths of donor–acceptor bonds between a given ligand and a series of electron acceptors, or between a given acceptor and a series of ligands. The systems we have been most interested in are those in which the electron acceptor is an element of Group III and this paper reviews the results obtained on the 1 : 1 complexes of boron trichloride and tribromide and the 1 : 1 and 1 : 2 complexes of gallium trichloride and tribromide.

Two methods have been used to determine the heat of formation of a crystalline complex: equilibrium vapour pressure measurements and direct reaction calorimetry. These give the heat of formation of the solid complex and from these, the heats of formation in the gas phase can be obtained in those cases where the relevant heats of sublimation and vaporization are known.

The equilibrium vapour pressure method is normally restricted to those cases where a solid complex dissociates either into a solid and a gas or into two gases. Experimentally the method simply involves synthesizing the complex in a vacuum line and then measuring its vapour pressure directly or on a spiral gauge. In this work it has been used mainly to cross-check the calorimetric measurements. As an example of its independent use, the dissociation pressure of triphenylmethyl tetrachloroborate was determined:

$$Ph_3C^+BCl_4^-{}_{(c.)} \rightleftharpoons Ph_3CCl_{(c.)} + BCl_{3(g.)}$$

The vapour pressure followed the relation $\log P(\text{atm}) = 4{\cdot}069 - 2077/T$. Hence the heat of the reaction is 9·51 kcal mole^{-1} and the entropy of formation $-18{\cdot}6$ cal mole^{-1} deg^{-1}.

The direct calorimetric method is more involved experimentally but is much more versatile. Many of the compounds studied were volatile, hygroscopic, or readily oxidized and it was necessary to design a calorimeter

to work in an inert atmosphere and over a range of temperature. In the final design[1] the mixing vessel was made from a B55 ground-glass cone and was 18 cm deep and 4 cm in diameter. It had a vacuum jacket to reduce heat losses. The calorimeter head was made from a B55 socket and carried six attachments; the stirrer and breaker rod had mercury seals and guide tubes; the thermocouple well and electrical heater for internal calibration during each experiment were of specially thinned glass; there was a drip feed for distilling or pouring in a known weight of ligand (which also served as the calorimetric liquid or " solvent "); and finally there was an inlet for dried nitrogen. The ground-glass joints carried sleeves of poly-(tetrafluoroethylene)—no grease was used.

Temperature changes were measured by a 15-junction copper–constantan thermocouple (0·0008°). The heater circuit for electrical calibration was of standard design; current from large-capacity storage batteries was stabilized by passage through a matched dummy heater for three hours before being switched through the true heater for a timed two minutes. The stirrer ran at 160 rev/min and gave no detectable heat of stirring. A formal assessment of the errors involved in timing, thermometry, and weighing shows that the expected precision is about 5 parts per thousand; in practice a reproducibility of 1–2 parts per thousand was frequently obtained.

The first complex studied was $GaCl_3.POCl_3$ (m.p. 118·5°)[1].

$$GaCl_{3(c.)} + (n + 1)POCl_{3(l.)} = GaCl_3.POCl_3 \text{ (in n } POCl_3);$$
$$-\Delta H = 11{\cdot}00 \pm 0{\cdot}01 \text{ kcal mole}^{-1}$$

$$GaCl_3.POCl_{3(c.)} + nPOCl_{3(l.)} = GaCl_3.POCl_3 \text{ (in n } POCl_3);$$
$$-\Delta H = 0{\cdot}83 \pm 0{\cdot}01 \text{ kcal mole}^{-1}$$

Hence

$$GaCl_{3(c.)} + POCl_{3(l.)} = GaCl_3.POCl_{3(c.)};$$
$$-\Delta H_f = 10{\cdot}17 \pm 0{\cdot}02 \text{ kcal mole}^{-1}$$

To calculate the heat of reaction in the gas phase, heats of sublimation are needed. A value of 15 kcal mole^{-1} for the complex was obtained manometrically. Other values are 8·5 kcal for $GaCl_{3(c.)}$ and 8·4 kcal for $POCl_{3(l.)}$. Thus

$$\tfrac{1}{2}Ga_2Cl_{6(g.)} + POCl_{3(g.)} = GaCl_3.POCl_{3(g.)}; \quad -\Delta H = 12{\cdot}1 \text{ kcal mole}^{-1}$$

and

$$GaCl_{3(g.)} + POCl_{3(g.)} = GaCl_3.POCl_{3(g.)}; \quad -\Delta H = 22{\cdot}6 \text{ kcal mole}^{-1}$$

The results indicate that the oxygen atom in phosphorus oxychloride is a better donor to gallium trichloride by 12 kcal than is the chlorine atom in dimeric gallium trichloride. The heat of the gas phase reaction between monomeric gallium trichloride and phosphorus oxychloride is 22·6 kcal mole^{-1}, but not all of this energy resides in the O—Ga bond, since the other bonds in the complex are modified during the process of donor–acceptor bonding.

Similar results for $GaCl_3.Et_2O$, m.p. 16°, and $GaCl_3.2Et_2O$, m.p. 9·0° are shown in the following equations:

$$GaCl_{3(c.)} + n\,Et_2O_{(l.)} = GaCl_3.2Et_2O \text{ (in excess ether)}; \quad -\Delta H = 21{\cdot}46 \pm 0{\cdot}06 \text{ kcal mole}^{-1}$$

$$GaCl_3.Et_2O_{(l.)} + n\,Et_2O_{(l.)} = GaCl_3.2Et_2O \text{ (in excess ether)}; \quad -\Delta H = 12{\cdot}12 \pm 0{\cdot}02 \text{ kcal mole}^{-1}$$

$$GaCl_3.2Et_2O_{(l.)} + n\,Et_2O_{(l.)} = GaCl_3.2Et_2O \text{ (in excess ether)}; \quad -\Delta H = 5{\cdot}98 \pm 0{\cdot}03 \text{ kcal mole}^{-1}$$

Hence

$$GaCl_{3(c.)} + Et_2O_{(l.)} = GaCl_3.Et_2O_{(l.)}; \quad -\Delta H_f = 9{\cdot}34 \pm 0{\cdot}08 \text{ kcal mole}^{-1}$$

$$GaCl_{3(c.)} + 2Et_2O_{(l.)} = GaCl_3.2Et_2O_{(l.)}; \quad -\Delta H_f = 15{\cdot}48 \pm 0{\cdot}09 \text{ kcal mole}^{-1}$$

$$GaCl_3.Et_2O_{(l.)} + Et_2O_{(l.)} = GaCl_3.2Et_2O_{(l.)}; \quad -\Delta H = 6{\cdot}14 \pm 0{\cdot}05 \text{ kcal mole}^{-1}$$

Addition of the first mole of ether evolves 9·34 kcal mole, whereas the second mole evolves only a further 6·14 kcal mole^{-1}. The heat of vaporization of the 1 : 1 complex was found to be 12·7 kcal mole^{-1}, which leads to the following data for the gas phase reactions:

$$\tfrac{1}{2}Ga_2Cl_{6(g.)} + Et_2O_{(g.)} = GaCl_3.Et_2O_{(g.)}; \quad -\Delta H = 11{\cdot}8 \text{ kcal mole}^{-1}$$

$$GaCl_{3(g.)} + Et_2O_{(g.)} = GaCl_3.Et_2O_{(g.)}; \quad -\Delta H = 22{\cdot}3 \text{ kcal mole}^{-1}$$

This last equation indicates that the heat of interaction of ethyl ether with monomeric gallium trichloride (22·3 kcal mole^{-1}) is more than twice its heat of reaction with boron trifluoride under the same conditions (10·9 kcal mole^{-1}).

The heats of formation of a series of complexes of gallium trichloride are compared in *Table 1*.

Table 1. Heat of formation of crystalline addition complexes from $GaCl_{3(c.)}$ and Ligand (l.)

Complex	$-\Delta H$(kcal mole^{-1})	*Complex*	$-\Delta H$(kcal mole^{-1})	
$GaCl_3.AsCl_{3(l.+c.)}$	1·4	$GaCl_3.Et_2O_{(c.)}$	9·3	6·2
$GaCl_3.PCl_{3(l.+c.)}$	3·4	$GaCl_3.2Et_2O_{(c.)}$	15·5	
$GaCl_3.POCl_{3(c.)}$	10·2	$GaCl_3.Py_{(c.)}$	29·8	11·7
$GaCl_3.MeCOCl_{(c.)}$	4·1	$GaCl_3.2Py_{(c.)}$	41·5	
$GaCl_3.Me_2CO_{(c)}$	15·3	$GaCl_3.Pip_{(c.)}$	33·7	18·4
		$GaCl_3.2Pip_{(c.)}$	52·1	

The values range from 1 to 52 kcal mole^{-1}. The low values for phosphorus trichloride, arsenic trichloride, and acetyl chloride correlate with the

observed instability of these compounds[2,3]. The heat of formation[4] of $GaCl_3.Me_2CO$(m.p.42·2°) is 15·3 kcal mole^{-1}, similar to the values found for the other oxygen-containing ligands mentioned above. The strongest donors investigated were pyridine and piperidine[5]. It is seen that for these the second mole of ligand is added with considerably less evolution of energy than the first and that piperidine is a stronger donor than pyridine. Equilibrium vapour pressure measurements afford a useful check on the calorimetric data here, for the solid 1 : 2 pyridine complex dissociates on heating to the solid 1 : 1 complex and pyridine vapour. From the temperature variation of the dissociation pressure and the vapour pressure of pyridine (Py) the heat of the reaction

$$GaCl_3.Py_{(c.)} + Py_{(g.)} = GaCl_3.2Py_{(c.)}$$

is 11·6 kcal, compared with the calorimetric value of 11·7 kcal.

The heat of formation of complexes of boron trichloride with nitrogen donors[6] is even greater than the energy of interaction of these ligands with gallium trichloride. Thus the heat of formation of $BCl_3.Py_{(c.)}$ is 40·7 kcal mole^{-1} and the heat of formation of the piperidine (Pip) complex $BCl_3.Pip_{(c.)}$ is 84·4 kcal mole^{-1}. At the other end of the scale is the very unstable compound between boron trichloride and acetyl chloride which only exists in the solid state[7]; above the m.p., −54°, it is completely dissociated and the heat of interaction of donor and acceptor to give the 1 : 1 liquid mixture is only 0·67 kcal mole^{-1}. When the entropy of complex formation is subtracted, the free energy of formation is substantially negative.

One of the most interesting observations made during this work was that, for a given ligand, the heat of formation of complexes of the tribromides was consistently greater than that for the corresponding trichlorides.

Table 2. Comparison of heats of formation of chloride and bromide complexes

Complex	$-\Delta H_f$ (kcal mole^{-1})	*Complex*	$-\Delta H_f$ (kcal mole^{-1})
$BCl_3.Py$	40·7	$BCl_3.Pip$	84·4
$BBr_3.Py$	45·6	$BBr_3.Pip$	114·5
$GaCl_3.Py$	29·8	$BCl_3.Me_2CO$	44·9*
$GaBr_3.Py$	34·5	$BBr_3.Me_2CO$	68·4*

* Heats of solution of halide in excess of ligand.

Some comparative data are set out in *Table 2*. They confirm the observations of Brown and Holmes on the sequence of acceptor strengths[7]: $BF_3 < BCl_3 < BBr_3$. Likewise the heat of formation of $GaCl_3.Py$ is significantly less than that of $GaBr_3.Py$ and the effect appears to persist even in the gas phase, when allowance has been made for the heats of sublimation and dimerization[5]. The most plausible explanation of the reversed sequence is that back donation of $p\pi$ electrons from the halogen into the vacant $p\pi$ orbital of the acceptor atom is greater for BCl_3 than for BBr_3, and hence the latter is a better acceptor of electrons from an external ligand because less reorganization energy from a planar to a tetrahedral configuration is required[8].

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VOL.
2
961

VOL.
2
1961

DISSOCIATION ENERGIES OF METAL–CARBON BONDS AND THE EXCITATION ENERGIES OF METAL ATOMS IN COMBINATION

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Volatile methyl compounds are formed by the majority of elements standing up to six places before a rare gas, so that as a class they represent all groups and periods of the Periodic System with the exception of Group I. Accordingly, the volatile methyls provide a particularly suitable class of compounds for a comparative study of the covalent bonds which the metals and non-metals concerned form with carbon; and this study in turn throws light on the magnitudes of the internal excitation energies possessed by these elements when engaged in covalent bonding. Former approaches to this problem have been almost entirely theoretical.

For convenience, the term " metal–carbon bond " will be used throughout this paper to denote all bonds of the type stated, whether the element linked to carbon is a metal or not.

MEAN DISSOCIATION ENERGIES

The heats of formation of the methyl compounds are required for calculating the mean metal–carbon dissociation energies, and, in the case of the highly reactive, spontaneously inflammable liquids or gases under discussion, their determination has provided unusual experimental difficulties. Two distinct lines of approach to this problem have proved successful. One, originally due to Skinner and his co-workers, has made use of bromination or iodination in non-aqueous media in specially designed apparatus. The other, employed by several investigators (including the present author), relies on a special technique for opening thin-walled glass ampoules in oxygen under pressure in a bomb calorimeter. Waddington and his collaborators have improved on this by introducing a rotating bomb, and this has been applied to the cases of the methyls of lead and sulphur. With all methods, considerable difficulty has been encountered in obtaining pure or even complete reactions, and a careful analysis of the products is in general necessary to obtain reliable heats of reaction. In some reactions a small element of uncertainty is introduced through the possibility of solid products being produced in an energy-rich form or doubtful crystalline state.

Notwithstanding these difficulties, it has usually proved possible by these methods to obtain heats of formation of the methyl compounds with an accuracy that corresponds to limits of error of ± 1 kcal or less in the mean dissociation energies of the metal–carbon bonds. However, in a number of cases uncertainties in auxiliary thermochemical data, especially heats of atomization, introduce larger possible errors.

To reduce the latter as far as possible, published values for the heats of formation have been recalculated, where appropriate, with the help of the most up-to-date thermochemical data, and a weighted mean selected in cases where there have been more than one determination. The values so obtained have been adjusted for the respective heats of vaporization of the liquid compounds at 25°C and listed for the gaseous species in *Table 1*. In the case of aluminium trimethyl, which is mainly dimeric in the vapour phase, adjustment has also been made for the heat of dimerization.

Table 1. Heats of formation of the volatile methyls and total energies of removal of methyl radicals

Methyl M $(CH_3)_n$	$-\Delta H_{f298\cdot15}$ *for gas* (kcal/mole)	*Ref.*	*Heat of atomization (25°C) of element* M (kcal/g-atom)	*Total energy of removal of all* Me *radicals* (kcal/mole)
$ZnMe_2$	− 13·26	1, 2	31·18	82·9
$CdMe_2$	− 26·4	1, 3	26·97	65·6
$HgMe_2$	− 20·78	4, 5	14·71	58·9
BMe_3	+ 29·8	1, 6	135·2	262·5
$AlMe_3$	+ 13·9*	1	77·4	188·8
$GaMe_3$	+ 9·1	7, 8	65·8	172·4
CMe_4	+ 39·67	9	171·4	341·1
$SiMe_4$	+ 49·5	10	105	284·5
$SnMe_4$	+ 11·2	10–12	71·9	213·1
$PbMe_4$	− 32·6	13	46·34	143·7
NMe_3	+ 4·1	14	112·95	214·5
PMe_3	+ 23·2	14	75·18	195·9
$AsMe_3$	− 3·7	15	60·64	154·4
$SbMe_3$	− 9·2	16	60·8	149·1
$BiMe_3$	− 45·8	17	49·5	101·2
OMe_2	+ 44·3	18	59·56	168·9
SMe_2	+ 8·88	19	66·75	140·6
ClMe	+ 20·634	20	28·942	82·1
BrMe	+ 9·563	21	26·85	68·9
IMe	− 3·6	5	25·48	54·4

* Monomeric species.

To calculate the mean dissociation energies, the heats of atomization of the respective elements are required, and the values used are likewise listed in *Table 1*. Also required is the heat of formation of the free methyl radical. This is best calculated from the bromination work[22] of Kistiakowsky and Van Artsdalen, which, when combined with the most recent thermochemical data, gives 101·6 kcal/mole at 0°K for $D(CH_3—H)$, corresponding to 102·5 at 25°C and −32·5 for the heat of formation of CH_3. From the latter value and the quantities listed in columns 2 and 4 of *Table 1*, the energy required to strip all the methyl radicals from each molecule, that is, to dissociate all the metal carbon bonds and leave the metal atom in its ground state, has been calculated (column 5). Experimental values are lacking for the methyls of indium, thallium, germanium, selenium, tellurium and fluorine.

VOL. 2 1961

The variation in the dissociation energies is more readily grasped by reference to *Table 2*, where the mean values per bond are arranged by groups and periods, according to the number of places the metal atom stands in front of a rare gas. An estimated value for $D(F—CH_3)$, based on the heats of formation of other organic fluorine compounds, has been added. This variation in the mean dissociation energy $D_m(M—C)$ must be ascribed principally to the change in the contribution made by the atom M.

Table 2. Mean M—C dissociation energies for the volatile methyls (in kcal)

	BMe_3 87·5	CMe_4 85·3	NMe_3 71·5	OMe_2 84·4	FMe (~ 120)
	$AlMe_3$ 62·9	$SiMe_4$ 71·1	PMe_3 65·3	SMe_2 70·3	ClMe 82·1
$ZnMe_2$ 41·5	$GaMe_3$ 57·5	$GeMe_4$ —	$AsMe_3$ 51·5	$SeMe_2$ —	BrMe 68·9
$CdMe_2$ 32·8	$InMe_3$ —	$SnMe_4$ 53·3	$SbMe_3$ 49·7	$TeMe_2$ —	IMe 54·4
$HgMe_2$ 29·5	$TlMe_3$ —	$PbMe_4$ 35·9	$BiMe_3$ 33·7		

Table 3. Valence-state energies for the free atoms (in eV)

	B 5·52	C 8·26	N 1·19	O 0·50	F 0·02
	Al 4·65	Si 6·22	P 0·70	S 0·30	Cl 0·04
Zn 4·49	Ga 5·75	Ge 6·8	As 0·67	Se 0·38	Br 0·15
Cd 4·26	In (5·5)	Sn —	Sb 0·57	Te 0·52	I 0·31
Hg 5·56	Tl 7·31	Pb —	Bi 0·86		

On viewing the dissociation energies from the point of view of the Periodic System as a whole, it is seen that, whereas there is a basic underlying regularity, in that, generally speaking, the dissociation energies decrease as the number of the period increases, being greatest in the upper right-hand corner and least in the lower left-hand, there are nevertheless marked irregularities. For example, relative to the contributions of its vertical neighbours, that of cadmium is low. Likewise the contribution of aluminium appears to be even more decidedly low. On the other hand the contributions of antimony and tin appear on a like basis to be higher than their position in the Periodic System would warrant. These irregularities are in general far too large to be ascribed to experimental error, but nowhere are they sufficiently great to change the vertical order in the magnitude of the dissociation energies.

Viewed horizontally, the contributions from silicon and gallium are seen to be distinctly high within their respective periods. However, the Group V elements probably all make weaker contributions than their Group IV neighbours, which is contrary to the general trend. Indeed, the deficiency is exceptionally large in the case of nitrogen, which makes by far the poorest contribution of all the first-row elements here considered. Quantitatively, the mean dissociation energy in NMe_3 is about 16 per cent lower than in CMe_4, instead of being a few per cent higher.

EXCITATION ENERGIES OF COMBINATION

The most reasonable explanation is that the forementioned irregularities, which appear to be superimposed on an underlying regularity, are due to the varying internal excitation energy as one passes from one atom to the next. This intra-atomic energy has frequently been referred to as the "valence-state energy", but this expression will not be used here in the foregoing sense, since it has also been employed for the energy levels of hypothetical states of free (uncombined) atoms, and it is necessary to make a distinction between the two uses. Accordingly, the term "excitation energy of combination" or "chemical excitation energy" is more appropriate where combined atoms are under discussion.

VOL. 2 1961

Logically, the mean dissociation energies derived thermochemically cannot be identified with the true or intrinsic bond energies of the respective bonds, because on the detachment of all the methyl groups the methyl radicals reorganize and the central atom falls back to the ground state with the release of the previously mentioned excitation energy. Hence the mean dissociation energy is a net quantity, and for the compound $M(CH_3)_n$ is less than the intrinsic bond energy E_i by an amount equal to the sum of R, the reorganization energy of the methyl radical, plus the nth part of V, the excitation energy of combination of the central atom M, that is,

$$E_i(\mathrm{M{-}C}) = D_m(\mathrm{M{-}C}) + R_{CH_3} + V_M/n$$

Whereas R may be nearly constant, or at least would not be expected to vary unsystematically, V unquestionably varies considerably with the number and nature of the electronic orbitals available on passing from one atom to its neighbour. Consequently, an anomalously low value of D_m will indicate that V for the central atom is higher than for its neighbours, and *vice versa*. This last statement is only valid if it can be assumed that the intrinsic bond energies (E_i values) vary systematically with the position of the central atom M in the Periodic System; but that they do so to an exceptionally good approximation is strongly implied by the orderly variation in other bond properties for the volatile methyl compounds. This conclusion is reached whether one turns to bond lengths or stretching force constants (only in the case of $HgMe_2$ is the metal–carbon force constant seriously anomalous).

In general, therefore, anomalously low D_m values correspond to higher V values; and that we are not dealing with valence-state energies of uncombined atoms is again emphasized by comparison of *Table 2* with *Table 3*, in which calculated[33–35] atomic valence-state energies are listed.

The two are seen to bear surprisingly little relation. For example, the D_m values in *Table 2* reveal that the excitation energy of the combined atom is much greater for nitrogen than for carbon, whereas for the free atom in the calculated valence state, the reverse is true.

INDIVIDUAL DISSOCIATION ENERGIES

For polyvalent atoms, further light may be shed on the excitation energy of combination by comparing the mean dissociation energies with individual dissociation energies. For certain of the methyls, it has proved possible to obtain individual dissociation energies from the measured activation energies in pyrolytic and other kinetic studies at elevated temperatures. Inherent in the method is an uncertainty of order $\pm RT$ and there may be larger errors, but that the method is capable of giving reliable values is seen in the case of methyl bromide, where the activation energy[26] of 67·0 ± 2 kcal agrees to within experimental error with the thermochemical dissociation energy of 68·9 kcal.

Experimental values of activation energies so far available are listed in *Table 4*. In general, where the compound decomposes by a first-order mechanism liberating methyl radicals, the activation energy can be identified with the energy absorbed in the process

$$MR_n \longrightarrow MR_{n-1} + R$$

Table 4. Dissociation energies of the first metal–carbon bonds of the methyls

Methyl	D_m (kcal)	D_1 (kcal) *estimated from kinetic data*				
$ZnMe_2$	41·5	47·2[27]				
$CdMe_2$	32·8	43·5[28]	45·8[29]			
$HgMe_2$	29·5	51·3[30]	51·5[31]	>42[32]	50·1[33]	57·9[34]
BMe_3	87·5	—				
$AlMe_3$	62·9	~ 78*[35]				
$GaMe_3$	57·5	—				
CMe_4	85·3	98·8*[36]	100*[37]	83·0*[38]		
$SiMe_4$	71·1	78·8[39]				
$SnMe_4$	53·3	82·4[40]				
$PbMe_4$	35·9	(>36·9[41])	23·5[42]	28·2[43]		
NMe_3	71·5	100·4*[44]	50·8[45]			
PMe_3	65·3	—				
$AsMe_3$	51·5	54·6[46]				
$SbMe_3$	49·7	57·0[47]				
$BiMe_3$	33·7	44·03[47]				
OMe_2	84·4	98·0*[48]	81·1[45]			
SMe_2	70·3	—				

* Value estimated on the basis of a chain mechanism of order 3/2.

that is to say, may be equated with D_1, the dissociation energy of the first metal–carbon bond. But this is apparently not the case with the first-row elements, where the methyl compounds decompose to give products containing double bonds. Thus neopentane gives mainly methane plus

isobutylene[26, 49], while NMe_3 and OMe_2 likewise give $CH_2{=}NCH_3$ [44] and $CH_2{=}O$ [45] among other products. Accordingly, the values for the first-row elements are not to be directly equated with dissociation energies, but in the higher periods the identification is reasonable, and here it is seen that the D_1 values are almost universally higher than the mean dissociation energies (the low values for $PbMe_4$ [42, 43] are associated with unreasonable pre-exponential factors and are probably erroneous, the true value almost certainly exceeding that for $PbEt_4$ [41]). $AlMe_3$ is a special case, in that its thermal decomposition is by a chain mechanism[35] of order 3/2. In such cases the apparent energy of activation E_a (45 kcal for $AlMe_3$) is equal to $\frac{1}{2}D_1 + E_2$, where E_2 is the activation energy of the step

$$CH_3 + M(CH_3)_n \longrightarrow CH_4 + CH_2M(CH_3)_{n-1}$$

CMe_4 ($E_a = 59{\cdot}4$ [36], 60 [37], 51·5 kcal[38]) and NMe_3 ($E_a = 59$ kcal[44]) both decompose by a precisely analogous mechanism of order 3/2, while OMe_2 ($E_a = 58{\cdot}5$ kcal[48]) apparently also has a three-halves order[50]. Since the amount of methane formed during photolysis of $AlMe_3$ at 29° and 120°C[35] suggests that E_2 here is ~6 kcal, whereas for CMe_4, NMe_3 and OMe_2 E_2 is known to be respectively 10·0 [51], 8·8 [52] and 9·5 kcal[52], the D_1 values for these four compounds are readily calculated and have been included in *Table 4*. The values derived for NMe_3 and OMe_2 by a mirror technique[45] would seem to be erroneous.

DISCUSSION

Although individual dissociation energies are lacking for a number of methyl compounds, while for others they are in some doubt, the most striking factor about the values listed in *Table 4*, taken as a whole, is that they differ markedly from the mean dissociation energies derived previously. In general they are larger, and this is precisely the state of affairs to be expected if the various polyvalent elements in Groups II to VI inclusive possess internal excitation energies in combination, since these elements would not return to the ground state on the rupture of a single bond, the state relative to which the mean dissociation energies are measured. The quantitative data discussed here therefore provide very strong evidence indeed for the reality of excitation energies of combined atoms, and this is perhaps the most important qualitative conclusion to be drawn from this study. The suggestion of the existence of such excitation energies is of course not new, but never before has it been verified for such a large number of elements.

It is, however, far more difficult to make any kind of quantitative pronouncement concerning this excitation energy. Quantitatively, the individual dissociation energies (D_1 values) will exceed the mean dissociation energies (D_m values) by an amount equal to the nth part of V, the excitation energy, less R', the energy of reorganization of the molecular fragment MR_{n-1} liberated on its formation from the molecule MR_n, that is

$$D_1 - D_m = V_M/n - R'$$

Merely to multiply $D_1 - D_m$ by n will give a fair estimate of the excitation energy V of element M only if R' is small.

VOL. 2 1961

This last condition is only likely to be realized with the elements in Group II. In this group, as in Groups III and IV, the excitation energy incorporates the energy of promotion of an s electron, as well as hybridization effects (which do not involve further electronic promotion). When only one of the bonds in, say, zinc dimethyl is ruptured, the zinc atom is not able to change its promoted state and recouple its electrons as an s^2 pair, neither will it change its valency angle. Accordingly R' may well be small with the methyl compounds of zinc, cadmium and mercury, in which case approximate values may be derived for V (*Table 5*) by ignoring R' and equating V to $2(D_1 - D_m)$. (Where alternative D_1 values are available, those derived from experiments with the unadulterated compound at higher pressures and lower temperatures have been selected as preferable.) The method has already been used by Pauling[53] in calculating the internal excitation energy of divalent oxygen.

Table 5. Approximate internal excitation energies of covalently bound zinc, cadmium and mercury

Element	*Compound*	D_1 (kcal)	D_m (kcal)	$V \simeq 2(D_1 - D_m)$ (eV)
Zn	$ZnMe_2$	47·2	41·5	~ 0·5
Cd	$CdMe_2$	43·5	32·8	~ 0·9
Hg	$HgMe_2$	51·3	29·5	~ 1·9

It is emphasized that these values for the excitation energies are tentative only. Nevertheless, they differ so widely from the values listed in *Table 3*, that it is again abundantly clear that we are not here dealing with the valence-state energies of uncombined atoms. Without making the most extravagant assumptions, no kind of agreement can be obtained, and, with the values listed in *Table 3*, the ZnMe, CdMe and HgMe radicals would be thermochemically unstable. Indeed, a fundamental reason can be suggested to explain why the two energies cannot be equated, namely that the method of calculating the valence-state energies of free atoms does not, indeed cannot, allow for the contribution to the internal excitation energy of the changed interaction terms (involving bonding and non-bonding electrons) caused by the additional electrons in the valence shell of the combined atom. Thus, for example, the energy of promotion of an s electron in molecular surroundings will not be the same as for a free atom.

In Groups III and IV, the reorganization energy R' may be appreciable, because, with the rupture of one bond, the bond angles and, conceivably, even the symmetry of the molecular fragment MR_{n-1} may change. It is difficult even to predict the sign of R', so that no reliable estimates of excitation energies are provided by the data for these groups. R' may be markedly negative in the case of $SnMe_4$, for example, as otherwise the intrinsic bond energy would be abnormally high compared with other bond properties.

In groups higher than IV, excitation energies of combination are not connected with the energies required to uncouple and promote individual s electrons, but with hybridization effects which involve a change in the

orbital of the s^2 pair equivalent to a partial promotion. The amount of this promotion can vary on the rupture of a bond, and this will affect R'. Accordingly, even with the divalent element oxygen, the position is far less favourable for numerical treatment than with zinc, and the excitation energy which can be derived from the data for OMe_2 by the foregoing method ($\sim$1·2 eV) will at best be semi-quantitative. The difference between this and Pauling's value[49] (0·78 eV) derived from old energy data for the H_2O molecule must—in so far as it is not due to sheer experimental error—be ascribed to the difference in reorganization energies of the OMe and OH radicals. If these are positive, as seems more likely in Groups V and VI where a partial demotion of the lone pairs of electrons is probably involved on the rupture of the first bond, then it may be better to regard both estimates as lower limits. Likewise the value that can be derived from NMe_3 for nitrogen ($\sim$3·8 eV) is probably best regarded as a lower limit. It is to be noted that the valence-state energy of the free nitrogen atom is very much smaller, though it must be emphasized that the latter is calculated for a non-hybridized state, whereas if hybridization were also taken into account for the free atom, the discrepancy would probably not be so large.

To conclude, a study of the known dissociation energies for the methyl compounds reveals that the internal excitation energy to be associated with an atom in a valence state is not the same for the combined as for the free atom. Until a theoretical method of reliably computing reorganization energies is available, inferences regarding the excitation energies of combined atoms remain qualitative, or, at best, semi-quantitative.

VOL. 2 1961

Note added in proof

For OMe_2, a recent further investigation[54] of the pyrolysis has provided experimental confirmation that the decomposition mechanism is of order 3/2, as considered likely in the foregoing (cf. *Table 4* and text). The observed activation energy, E_a, is 55·6 kcal, which, with $E_2 = 9{\cdot}5$ kcal, furnishes the improved value, $D_1 = 92{\cdot}2$ kcal.

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VOL
2
1961

THE THERMOCHEMISTRY OF SOME ORGANO-PHOSPHORUS COMPOUNDS

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DETERMINATION OF HEATS OF FORMATION

In recent years a certain amount of thermochemical data has been accumulated for organo-phosphorus compounds. The data have been obtained by measuring heats of reaction by two general methods:

(*a*) combustion calorimetry, involving degradative oxidation; and
(*b*) reaction calorimetry, where the heats of such reactions as hydrolysis, aminolysis, and partial oxidation have been measured.

As examples of degradative oxidation, we may mention the following combustion reactions, the heats of which have been measured recently[1]:

$$PPh_{3(c.)} + 23\ O_{2(g.)} \longrightarrow H_3PO_{4(c.)} + 18\ CO_{2(g.)} + 6\ H_2O_{(l.)};$$
$$-\Delta H_c^\circ = 2463{\cdot}3 \pm 2{\cdot}3 \text{ kcal/mole}$$

$$OPPh_{3(c.)} + 22{\cdot}5\ O_{2(g.)} \longrightarrow H_3PO_{4(c.)} + 18\ CO_{2(g.)} + 6\ H_2O_{(l.)};$$
$$-\Delta H_c^\circ = 2393{\cdot}4 \pm 3{\cdot}0 \text{ kcal/mole}$$

$$OP(OEt)_{3(l.)} + 9\ O_{2(g.)} \longrightarrow H_3PO_{4(c.)} + 6\ CO_{2(g.)} + 6\ H_2O_{(l.)};$$
$$-\Delta H_c^\circ = 982{\cdot}9 \pm 1{\cdot}3 \text{ kcal/mole}$$

From these heats of combustion, the heats of formation of the organo-phosphorus compounds may be calculated in terms of the heat of formation of crystalline orthophosphoric acid, taken as[2] $-306{\cdot}2$ kcal/mole, and the generally accepted values for carbon dioxide and water[2]. The values obtained are

$$\Delta H_f^\circ(PPh_{3(c.)}) = +54{\cdot}3 \pm 2{\cdot}3 \text{ kcal/mole};$$
$$\Delta H_f^\circ(OPPh_{3(c.)}) = -15{\cdot}6 \pm 3{\cdot}0 \text{ kcal/mole};$$
$$\text{and } \Delta H_f^\circ(OP(OEt)_{3(l.)}) = -297{\cdot}5 \pm 1{\cdot}3 \text{ kcal/mole}$$

After the combustions, the phosphoric acid was, in fact, in aqueous solution, so that a correction for the heat of solution was necessary. These combustions were made in a static bomb, and as a result the concentration of phosphoric acid probably varied considerably in different parts of the bomb, leading to the comparatively large error of $\pm 0{\cdot}1$ per cent, associated with the heats of combustion. This error could be reduced very considerably by using a rotating bomb technique.

A number of organo-phosphorus compounds undergo reactions which can be studied conveniently in a simple reaction calorimeter. An example

of such a reaction, the heat of which has been measured recently[3], is the hydrolysis of the phosphinimine, $Ph_3P{=}NEt$,

$$Ph_3P{=}NEt_{(c.)} + H_2O_{(l.)} + HCl_{(aq.)} \longrightarrow OPPh_{3(c.)} + EtNH_2 \,.\, HCl_{(aq.)};$$
$$\Delta H = -11{\cdot}7 \pm 0{\cdot}3 \text{ kcal/mole}$$

In this case the heat of formation of the phosphinimine

$$\Delta H_f^\circ(Ph_3P{=}NEt_{(c.)}) = +27{\cdot}0 \pm 3{\cdot}5 \text{ kcal/mole}$$

is calculated from the heat of formation of triphenylphosphine oxide, which is known from the combustion data, in terms of the heat of formation of orthophosphoric acid.

A useful intermediate in the reaction calorimetry of phosphorus compounds is phosphorus trichloride. The heat of formation of this is known from the heat of hydrolysis, carried out under oxidizing conditions, to orthophosphoric acid[4], *viz.*,

$$PCl_{3(l.)} + 4\,H_2O_{(l.)} + Br_{2(aq.)} \longrightarrow H_3PO_{4(aq.)} + 3\,HCl_{(aq.)} + 2\,HBr_{(aq.)};$$
$$\Delta H = -137{\cdot}9 \text{ kcal/mole}$$

The heat of formation of triethyl phosphate has been determined, in terms of that of phosphorus trichloride, from measurements of the heats of the following reactions, in which phosphorus trichloride is esterified to triethyl phosphite[5], which is then oxidized to triethyl phosphate[6]:

$$PCl_{3(l.)} + 3\,EtOH_{(l.)} + 3\,PhNH_{2(l.)} \longrightarrow P(OEt)_{3(l.)} + 3\,PhNH_2 \,.\, HCl_{(c.)};$$
$$\Delta H = -74{\cdot}8 \text{ kcal/mole}$$

$$P(OEt)_{3(l.)} + H_2O_{2(l.)} \longrightarrow OP(OEt)_3 + H_2O_{(l.)};\ \Delta H = -116{\cdot}3 \text{ kcal/mole}$$

From these data, the value $\Delta H_f^\circ(OP(OEt)_{3(l.)}) = -297{\cdot}8 \pm 3{\cdot}0$ kcal/mole is derived, which is in close agreement with that obtained by combustion calorimetry.

Other thermochemical data for organo-phosphorus compounds include $\Delta H_f^\circ(P(NEt_2)_{3(l.)}) = -66{\cdot}8 \pm 2{\cdot}5$ kcal/mole, obtained by measuring the heat of reaction of phosphorus trichloride with diethylamine, in which the amino-phosphine is formed[7]. Also the heats of combustion of some phosphonitrilic compounds have been determined, and the heats of formation dervied[8]: $\Delta H_f^\circ((PNPh_2)_{4(c.)}) = +40{\cdot}7 \pm 11{\cdot}5$ kcal/mole and $\Delta H_f^\circ((PNMe_2)_{3(c.)}) = -125{\cdot}2 \pm 2{\cdot}7$ kcal/mole.

All these heats of formation are based on the heat of formation of orthophosphoric acid. This is derived from the work of Thomsen[9], in 1882, the overall accuracy of which it is difficult to assess: some independent measurements by Giran[10], in 1903, confirm Thomsen's value, so that it might be accepted with some confidence. However, it would seem advisable to redetermine the value with the advantage of modern thermochemical methods.

DISSOCIATION ENERGIES

The heats of formation may be used to find the strength of the bonding between phosphorus and other atoms. A measure of this, for trivalent

phosphorus compounds of the type PR_3, is the mean bond dissociation energy D_m(P—R). This is defined as one-third of the heat of the gas-phase reaction

$$PR_{3(g.)} \longrightarrow P_{(g.)} + 3\,R_{(g.)}$$

in which the compound is dissociated into phosphorus atoms and atoms or radicals R. *Table 1* shows some mean bond dissociation energies, together with the heats of formation used in the calculations.

Table 1. Mean bond dissociation energies in PR_3, based on[13] $\Delta H_f^\circ(P_{(g.)}) = 75{\cdot}3$ kcal/g-atom

Compound	$\Delta H_f^\circ(PR_{3(g.)})$ (kcal/mole)	*Ref.*	$\Delta H_f^\circ(R_{(g.)})$ (kcal/mole)	*Ref.*	D_m(P—R)* (kcal/mole)
PCl_3	− 66·6	4	+ 28·94	13	76·2
PBr_3	− 29·7	11	+ 26·7	13	61·7
$P(OEt)_3$	− 194·1	1, 4	− 8·1	14	81·7
$P(NEt_2)_3$	− 52·3	7	+ 34·9	*	77·4
PMe_3	− 23·2	12	+ 32·5	14	65·3
PPh_3	+ 72·4	1	+ 70	14	71·0

* Calculated from $\Delta H_f^\circ(Et_2NH_{(g.)}) = -17{\cdot}0$ kcal/mole, assuming[15] $D(Et_2N—H) = D(H_2N—H) = 104$ kcal/mole.

The heats of dissociation of the phosphoryl compounds to the trivalent phosphorus compounds, D(P=O), represented by the following equation, are especially interesting:

$$OPR_{3(g.)} \longrightarrow O_{(g.)} + PR_{3(g.)}$$

In some cases the heat of the reverse process, that is oxidation of the PR_3 molecule, has been measured. Otherwise these dissociation energies can be calculated from differences between the heats of formation of OPR_3 and PR_3 molecules.

It has been suggested[6] that the OPR_3 molecule should be regarded as a tetrahedral structure $\bar{O}—\overset{+}{P}R_3$, modified by back co-ordination from the $2p_x^2$ and $2p_y^2$ orbitals of O^- to the vacant $3d_\pi$ orbitals of P^+, thus giving $\bar{O}—\overset{+}{P}$ triple bond character, with the further possibility of back co-ordination to P from the R atoms or groups, if these have donor electrons. For convenience, we shall continue to designate the dissociation energy of the bond D(P=O), though bearing in mind this additional π-bonding.

Values of D(P=O) for a number of phosphoryl compounds are shown in *Table 2*. The variation in these dissociation energies reflects changes in the strength of both the phosphoryl bond, as suggested by the shift in Raman frequency and infra-red wavelength of this bond on changing the R groups, and also in the strength of the P—R bonds.

In the series (*a*) $OPBr_3$, $OPCl_3$, OPF_3, it is seen that D(P=O) increases with increasing electronegativity of R. Along the series (*b*) OPF_3, $OP(OEt)_3$, $OP(NEt_2)_3$, there is also an increase in D(P=O), which is unexpected in terms of electronegativity. A possible explanation is that back co-ordination from the R groups to the phosphorus atom is increased in $\bar{O}—\overset{+}{P}R_3$, as compared with PR_3, causing a strengthening of the P—R

bonds in the phosphoryl compound, which will be included in $D(P{=}O)$. It is known that the power to back co-ordinate is greater for nitrogen than oxygen, which is greater, in turn, than that for chlorine[16]. This effect would seem to offset any reduction in $D(P{=}O)$ due to the decrease in electronegativity along the series fluorine, oxygen, nitrogen.

Table 2. Gas-phase dissociation energies (in kcal/mole): $APR_3 \longrightarrow A + PR_3$

Basis of estimate	$D(P{=}O)$	*Ref.*
(*a*) ΔH oxidation PF_3 to OPF_3	129·8	20
ΔH_f° PCl_3 and $OPCl_3$	127·5	4
ΔH_f° PBr_3 and $OPBr_3$	124·9	11
(*b*) ΔH oxidation PF_3 to OPF_3	129·8	20
ΔH_f° $P(OEt)_3$ and $OP(OEt)_3$	150·7	1, 5, 6
ΔH_f° $P(NEt_2)_3$ and $OP(NEt_2)_3$	160*	7
ΔH oxidation PPr_3 to $OPPr_3$	138·3	6
ΔH_f° PPh_3 and $OPPh_3$	128·4	1
	$D(P{=}S)$	
(*c*) ΔH oxidation $P(OEt)_3$ to $SP(OEt)_3$	81·6	21
ΔH oxidation PPr_3 to $SPPr_3$	82·6	21

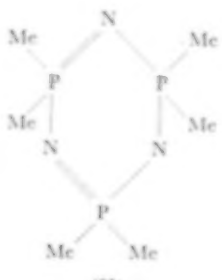
* $\Delta H_f^\circ(OP(NEt_2)_{(g)})$ estimated from bond energy data, see Ref. 7.

Although there are fewer data available for the thiophosphoryl compounds (*c*), the variation in $D(P{=}S)$ appears to be considerably less than $D(P{=}O)$ in phosphoryl compounds. This is expected, since the smaller electronegativity difference between sulphur and phosphorus, than between oxygen and phosphorus, will make the bonding in thiophosphoryl compounds less susceptible to the nature of the R groups.

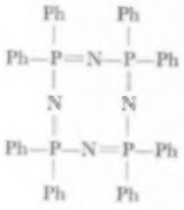
BOND ENERGIES IN PHOSPHONITRILIC COMPOUNDS

The thermochemistry of the phosphonitrilic compounds shown below is best interpreted in terms of bond energies. The heat of formation of (I) has been given by Paddock and Searle[17] as $-178{\cdot}1 \pm 3$ kcal/mole, from some preliminary measurements; the heats of formation of (II) and (III) have been referred to previously[8]. From these figures it is possible to calculate the sum of the bond energies in the " ring unit ", $E(R_2P{=}N{-}P)$.

(I)



(II)



(III)

This is simply done by taking one-third of the heat of formation of the compounds (I) and (II) from the atoms, or one-quarter of the heat of formation of (III). Now it is unlikely that the bond energies (or group energies where R = Me or Ph) of the P—R bonds (or groups) in the phosphonitrilic molecules will be less than in the corresponding PR_3 compounds, and the indications of the preceding section are that the bond energies will be slightly greater in the phosphonitrilics. Substituting the values for E(P—R), derived from PR_3 molecules, in the ring unit gives a *maximum* value for the sum of the single and double phosphorus–nitrogen bond energies, E(P=N—P). These values are shown in *Table 3.*

Table 3. Bond energies in phosphonitrilic compounds (in kcal/mole). E(P—R) = $\frac{1}{3}\Delta H_f^\circ$ $(PR_{3(g.)})$*

Compound	$\Delta H_{f(g.)}^\circ$	$E(R_2P{=}N{-}P)$	E(P—R)	E(P=N—P)
$(PNCl_2)_3$	− 178·1	305·4	76·2	153
$(PNMe_2)_3$	− 107·1	878·3	360·0	158
$(PNPh_2)_4$	+ 58·7	2745·1	1286·8	172

*The heat of formation of the gaseous compound from the atoms.

It would be interesting to compare E(P=N—P) with the sum E(P=N) + E(P—N), the single and double bond energies, found in other molecules, since it has been suggested that these inorganic " aromatic " molecules will have a resonance energy[18].

Values for the bond energy of the phosphorus–nitrogen double bond, E(P=N) can be calculated from the heats of formation of the gaseous phosphinimines $Me_3P{=}NEt$ and $Ph_3P{=}NEt$. These have been given[3] as $-21{\cdot}9 \pm 2{\cdot}6$, and $+45{\cdot}0 \pm 5$ kcal/mole, respectively. Assuming that the bond energies of the groups Me_3P and Ph_3P are the same in the phosphinimines as in the trivalent compounds trimethylphosphine and triphenylphosphine, the bond energies are calculated as E(P=N) = 69·7 kcal/mole in trimethylphosphinimine, and E(P=N) = 98·4 kcal/mole in triphenylphosphinimine. It is interesting to note the large difference, of 28·7 kcal/mole, between these two values.

For the phosphorus–nitrogen single bond, we have the value E(P—N) = 66·8 kcal/mole, calculated from the heat of formation of gaseous trisdiethylaminophosphine, $P(NEt_2)_3$. Since we have used E(P—R) values derived from trivalent PR_3 molecules to calculate the bond energy of the ring unit E(P=N—P), and also to derive E(P=N) values, it seems reasonable to use this value for E(P—N) found in a trivalent compound. Thus, the sum E(P=N) + E(P—N) is calculated as 136·5 kcal/mole, when the phosphorus atom in the phosphinimine is methyl-substituted; and 165·2 kcal/mole when it is phenyl-substituted.

The values of E(P=N—P) in the corresponding phosphonitrilic compounds are 158 and 173 kcal/mole, so that the " resonance " energy of the ring unit is 21 kcal/mole for the methyl-substituted compound and 7 kcal/mole for the phenyl-substituted compound. Hence, the resonance energy of the six-membered ring system, $(PNMe_2)_3$, is ~60 kcal/mole, and of the eight-membered ring system, $(PNPh_2)_4$, is ~28 kcal/mole.

Here, as in the calculation of all resonance energies, the values depend upon the choice of the standard, non-resonating compound with which the resonance structure is compared. In these cases it is the phosphinimines which are taken as the reference compounds, despite the fact that there is probably considerable electron delocalization involving the phosphorus 3*d*-electrons and the π-electrons of the phenyl groups.

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VOL. 2 1961

THERMOCHEMISTRY OF ORGANIC FLUORINE COMPOUNDS AND CARBON COMPOUNDS OF METALS BY ROTATING-BOMB CALORIMETRY*

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Rotating-bomb calorimetry was first applied to organic compounds that contain chlorine, bromine, or sulphur. Techniques developed for these classes of compounds, mostly at the University of Lund and at the Bureau of Mines in Bartlesville, have been described in the book *Experimental Thermochemistry*[1]. The development of rotating-bomb methods made accurate combustion calorimetry feasible for other classes of compounds besides those of chlorine, bromine, or sulphur. Two of these other classes of compounds have received attention in the Bureau of Mines laboratory in recent years, namely: (a) organic fluorine compounds and (b) organometallic compounds and other carbon compounds of metals. Techniques developed for rotating-bomb calorimetry of these two classes of compounds are reviewed in this paper.

ORGANIC FLUORINE COMPOUNDS

Chemistry of the bomb process

In combustion calorimetry of an organic fluorine compound, $C_aH_bO_cN_dF_e$, the sample reacts with oxygen in a calorimetric bomb containing some water. The products are some or all of the following: CO_2, H_2O, N_2, HNO_3, HF, and CF_4. Traces of HNO_3 are formed from nitrogen impurity in the oxygen with which the bomb is charged, even if the compound itself does not contain nitrogen. If the compound is not highly fluorinated, all of the fluorine appears in the products as HF. However, if the compound is highly fluorinated, 80 per cent or more of the fluorine may appear in the products as CF_4. Examination of combustion products for fluorine-containing compounds other than hydrogen fluoride and tetrafluoromethane has always given negative results.

Rotating-bomb calorimeter, bomb, and fittings

The calorimeter[2] used for organic fluorine compounds embodies several improvements over earlier models, the most noteworthy of which is provision for continuous rotation of the bomb to the end of the calorimetric experiment. Continuous rotation assures homogeneity and equilibrium of the final contents of the bomb and simplifies the correction for energy generated by rotation of the bomb.

* Contribution No. 83 from the Thermodynamics Laboratory.

Owing to the corrosive nature of the hydrofluoric acid in the combustion products, a platinum-lined bomb was used. The bomb was placed in the calorimeter in the inverted position. The crucible and all other internal fittings of the bomb were made of platinum. Slight attack of the platinum crucible occurred during combustion of highly fluorinated samples, but the amount of attack was scarcely significant thermochemically.

Containers for volatile samples

Glass ampoules could not be used as containers for volatile fluorine compounds, because the glass would react with the hydrogen fluoride in the combustion products. In early work, fused-silica ampoules were used, and thermochemical corrections were applied for reaction between the silica and hydrogen fluoride. In later work, volatile samples were sealed in polyester film bags[8]. These containers are impervious to compounds of all degrees of fluorination, and they undergo complete combustion along with the samples they contain.

Experimental procedures

In general, the calorimetric procedures were similar to those of rotating-bomb methods for other classes of compounds. The bomb initially contained water, usually 10 ml. Carbon dioxide having been expelled from the solution, the total acidity of the final bomb contents was determined by acid–base titration, loss of hydrogen fluoride being prevented by converting it to non-volatile HF_2^- ion. Nitric acid was determined by Devarda's method. Hydrogen fluoride was determined as the total acidity (corrected for nitric acid), and tetrafluoromethane was then determined by difference.

VOL. 2 1961

Comparison experiments

Reduction of the calorimetric results to standard states could not be made rigorously because certain data, particularly values of the solubility and heat of solution of carbon dioxide in aqueous hydrofluoric acid as functions of concentration, were lacking. Errors from inexact reduction to standard states were minimized by use of comparison experiments. In these experiments, the sample was benzoic acid and either succinic acid or a hydrocarbon oil, and the bomb initially contained a solution of hydrofluoric acid. The amounts were selected so that the evolution of energy, the amount of carbon dioxide formed, and the amount and concentration of the final bomb solution all were nearly the same as in the combustion experiment with the fluorine compound. The comparison experiments were used to determine an *apparent* energy equivalent of the calorimetric system. The value of the *apparent* energy equivalent was used to compute the heat of combustion of the fluorine compound. In the result so obtained, errors from inexact reduction to standard states were eliminated or made much smaller by cancellation.

Results

Values of heat of formation for 15 organic fluorine compounds determined by rotating-bomb calorimetry are listed in *Table 1*. These derived results were obtained from the experimental values of the heat of combustion by

use of presently accepted values for the heat of formation of $CO_{2(g.)}$ $H_2O_{(l.)}$ and HF (in aqueous solution)[5] and the value[6], $\Delta H^\circ_{298\cdot15} = -218\cdot_3$ kcal mole^{-1} for CF_4. If the heat of vaporization has been determined, the heat of formation is given for the vapour state as well as for the condensed state.

Table 1. Heat of formation of organic fluorine compounds

$a\,C_{(c.)}(\text{graphite}) + b/2\,H_{2(g.)} + c/2\,O_{2(g.)} + d/2\,N_{2(g.)} + e/2\,F_{2(g.)} = C_aH_bO_cN_dF_{e(c.\ l.\ or\ g.)}$

Compound	$\Delta H^\circ_{f\,298\cdot15}$ (kcal mole^{-1})			*Ref.*
	Crystals	*Liquid*	*Gas*	
o–Fluorobenzoic acid	$-134\cdot3_8$			2
m–Fluorobenzoic acid	$-137\cdot8_4$			2
p–Fluorobenzoic acid	$-138\cdot9_5$			2
4–Fluorotoluene		$-43\cdot4_3$	$-34\cdot0$	4
Fluorobenzene		$-34\cdot7_5$	$-26\cdot4_8$	2
1,2–Difluorobenzene		$-76\cdot2_9$	$-67\cdot6_5$	4
1,3–Difluorobenzene		$-79\cdot6_3$	$-71\cdot3_7$	4
1,4–Difluorobenzene		$-79\cdot2_3$	$-70\cdot7_0$	4
Benzotrifluoride		$-147\cdot8_5$	$-138\cdot8_7$	2
m–Fluorobenzotrifluoride		$-193\cdot2_4$	$-184\cdot1_7$	3
Perfluoropiperidine		$-482\cdot_9$	$-475\cdot_9$	4
Perfluoromethylcyclohexane		$-683\cdot_4$	$-675\cdot_3$	3
Perfluoroethylcyclohexane		$-778\cdot_9$	$-769\cdot_7$	3
Poly(tetrafluoroethylene)	$-193\cdot_5$*			2
Perfluoro-n-heptane		$-797\cdot_7$	$-789\cdot_0$	3

* kcal monomole^{-1} for material that had received no heat treatment.

ORGANO-METALLIC AND RELATED COMPOUNDS

Chemistry of the bomb process

Four carbon compounds of metals were studied by rotating-bomb calorimetry: tetramethyl-lead[7], tetraethyl-lead[8], lead oxalate[8], and di-manganese decacarbonyl[9]. Solid products from combustion of these compounds were dissolved by a solution in the bomb. For lead compounds, the solution contained nitric acid and a little arsenious acid. This solution, in the presence of oxygen under pressure, dissolved all solid lead compounds to give Pb^{2+} in solution. For the manganese compound, the solution contained nitric acid and a little hydrogen peroxide; this solution dissolved all solid manganese compounds to give Mn^{2+} in solution. Rotation of the bomb after the combustion reaction was finished assured the rapid solution of the solid products wherever they might be in the bomb.

Lead oxalate alone would not sustain combustion, and use of an equal mass of hydrocarbon oil as promoter was necessary to obtain complete combustion. Tetramethyl lead, on the other hand, would detonate to produce "soot" and other incompletely oxidized products, and dilution with a hydrocarbon oil as moderator was necessary to obtain smooth combustion which went to completion. The heat of dilution was determined in separate experiments. Tetraethyl-lead had satisfactory combustion characteristics.

Two complications were encountered with the manganese compound. First, a lower-than-normal pressure of oxygen was needed to obtain the

solid products in a finely divided state suitable for solution; unfortunately, at the required lower oxygen pressure, a " carbon residue " was formed. Second, catalytic decomposition of the hydrogen peroxide in the bomb solution took place in the presence of manganous ion. However, appropriate thermochemical corrections were possible for both of these complicating effects.

Rotating-bomb calorimeter, bomb, and fittings

The same calorimeter was used for the organo-metallic and related compounds as was used for the organic fluorine compounds. The provision for continuous rotation of the bomb was particularly necessary because of the relatively long time required to dissolve the solid products.

A bomb made of nickel–chromium alloys was used because the thin lining of a platinum-lined bomb might be damaged by spattering of molten metal or oxides. However, some interior fittings less liable to such damage were made of platinum. To prevent short circuiting of the ignition current through the conducting bomb solution, the insulated electrode was mounted on a post integral with the head of the bomb. When the bomb was in the calorimeter in the inverted position, the top of the post was above the surface of the bomb solution.

A platinum crucible was satisfactory for the manganese compound. However, platinum crucibles were not inert to the combustion products of the lead compounds, so fused-silica crucibles were used. The fused silica fluxed somewhat with the solid lead compounds, but the amounts of the products (lead silicate and aqueous silicic acid) could be determined and appropriate thermochemical corrections applied for the fluxing reaction.

Containers for volatile samples

Samples of tetraethyl-lead were enclosed in unsealed ampoules of fused silica. As the ampoules were of the same material as the crucibles, single thermochemical corrections could be made for fluxing with both the crucible and the fragments from the ampoules. Samples of tetramethyl-lead, diluted with hydrocarbon oil, were sealed in polyester film bags similar to those used for the organic fluorine compounds. No containers were needed for the non-volatile solids, lead oxalate and dimanganese decacarbonyl.

Experimental procedures

In general, the calorimetric procedures were similar to those of rotating-bomb methods for other classes of compounds. The bomb initially contained the solution (usually 50 ml) to dissolve the solid products. The reaction period was longer than normal because of the time required for the solid products to dissolve. When the calorimetry was complete, the final bomb contents were analysed chemically. The amount of reducing agent (arsenious acid or hydrogen peroxide) remaining was determined, and all other determinations necessary for application of thermochemical corrections or verifying the chemistry of the bomb process were made.

VOL. 2 1961

Comparison experiments

Use of comparison experiments for fluorine compounds has already been described. Comparison experiments for the organo-metallic and related compounds were even more important because of the greater volume of bomb solution and therefore larger corrections for dissolved carbon dioxide. In these comparison experiments, the sample was benzoic acid or hydrocarbon oil or both, in amounts selected so that the evolution of energy and the amount of carbon dioxide formed, or at least the latter, were the same as in the combustion experiment. An inorganic compound of the metal, solid $Pb(NO_3)_2$ or a concentrated solution of $Mn(NO_3)_2$, was placed in a second crucible in the bomb. (The hygroscopic $Mn(NO_3)_2$ solution was enclosed in a glass ampoule.) The amount and composition of the initial bomb solution was such that the final bomb solution duplicated the one in the combustion experiment. The comparison experiments, in addition to minimizing errors from inexact reduction to standard states, also allow the combusion reaction to be referred to the inorganic compound of the metal as product, with the latter in a physical state for which the heat of formation is well known. Possible errors because the calorimetry is not strictly a substitution method are also cancelled by use of comparison experiments.

Results

Values of the heat of formation of the four organo-metallic or related compounds, determined by rotating-bomb calorimetry, are listed in *Table 2*. These derived results were obtained from the experimental values

Table 2. Heat of formation of organo-metallic and related compounds
$a\,C_{(c)}$. (graphite) $+ b/2\,H_{2(g.)} + c/2\,O_{2(g.)} + d\,M_{(c.)} = C_aH_bO_cM_{d\,(c.\ l.\ or\ g.)}$ M is Pb or Mn

Compounds	$\Delta H^\circ_{f\,298\cdot15}$ (kcal mole^{-1})			*Ref.*
	Crystals	*Liquid*	*Gas*	
Tetramethyl-lead		23·5	32·6	7
Tetraethyl-lead		12·8		8
Lead oxalate	− 203·2			8
Dimanganese decacarbonyl	− 400·9			9

of the heat of combustion by use of presently accepted values for the heat of formation of $CO_{2(g.)}$, $H_2O_{(l.)}$, HNO_3 (in aqueous solution), $Pb(NO_3)_{2(c.)}$, and $Mn(NO_3)_2$ (in aqueous solution)[5].

DISCUSSION

The rotating-bomb method can be used for accurate combustion calorimetry of most solid or liquid organic fluorine compounds. The rotating-bomb method also makes possible accurate combustion calorimetry of organo-metallic and related compounds, although special problems have to be solved for compounds of each particular metal and even for individual compounds of a given metal. The thermochemistry of both classes of compounds is now on a sound experimental basis.

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VOL.
2
1961

THERMOCHEMIE ISOMERER CHLORTOLUOLE

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Vor einigen Jahren haben wir das thermochemische Verhalten der isomeren Hexachlorcyclohexane untersucht[1]. Es wurde geprüft, ob die in den Patentschriften beanspruchte thermochemische Umwandlung der als Insektizid unwirksamen Isomeren in das hochwirksame und technisch so wichtige γ-Isomere thermodynamisch möglich ist. Neben den Verbrennungswärmen, die zeigten, dass das γ-Isomere leider das energiereichste unter den bei der Photochlorierung des Benzols hauptsächlich entstehenden Hexachlorcyclohexanen ist, wurden auch die Lösungswärmen der Isomeren in verschiedenen Lösungsmitteln sowie die Aktivitäten gemessen. Dabei wurden im gleichen Lösungsmittel relativ grosse Unterschiede zwischen den Isomeren gefunden, die auf den verschiedenen Werten der Schmelzwärmen beruhen konnten. Es sind daher flüssige isomere Verbindungen untersucht worden, bei denen die Schmelzwärmen keinen Anteil an den Messergebnissen haben. Die Versuche wurden mit den drei isomeren Chlortoluolen ausgeführt. Von deren Mischsystemen mit Benzol sind die Aktivitäten, die Mischvolumina und die Mischungswärmen gemessen worden.

EXPERIMENTELLER TEIL

Aktivitäten

Die Aktivitäten sind durch statische Messung der Dampfdruckerniedrigung der Lösung gegenüber dem reinen Lösungsmittel bestimmt worden. Die Messungen wurden nach einer Differentialmethode von F. Klages und K. Möhler[2] ausgeführt. Als Manometerflüssigkeit wird hierbei das reine Lösungsmittel verwendet. Dieses Verfahren hat den Vorteil, dass die trotz Entlüftung von Apparatur und Substanzen stets vorhandenen geringen Luftmengen sich sowohl auf Lösung wie auf Lösungsmittel gleich auswirken. Ausserdem erlaubt das Lösungsmittelmanometer eine etwa zwanzigmal grössere Ablesegenauigkeit als das Quecksilbermanometer.

Die verwendete Apparatur ist in *Bild 1* schematisch dargestellt. Sie besteht aus der Entlüftungsanlage (*a*) und dem eigentlichen Differentialmanometer (*b*). Um das Lösungsmittel zu entlüften, wird es in dem Kolben A bis unter seinen Schmelzpunkt abgekühlt. Der Apparaturteil (*a*) wird dann mit einer Quecksilberdiffusionspumpe auf 10^{-5} Torr evakuiert. Der Entlüftungsgrad kann an einem McLeod-Manometer G überprüft werden. Nach Beendigung der Entlüftung wird Hahn D geschlossen, das Lösungsmittel aufgetaut und von A nach B destilliert. Der Kühler C wird während der Destillation mit einer Eis-Kochsalz-Sole gespeist. Der gleiche Entlüftungsprozess wird nochmals ausgeführt, so dass sich am Ende das Lösungsmittel wieder im Kolben A befindet.

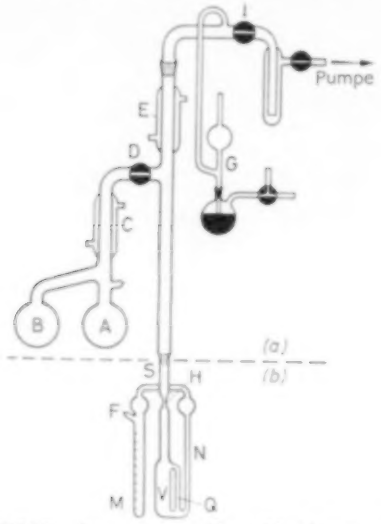

Bild 1. Apparatur zur Dampfdruckmessung

Dieser Behandlung schliesst sich eine Feinentlüftung an: Das Lösungsmittel wird bei laufender Pumpe am Rückflusskühler C destilliert. Dabei sammeln sich die letzten Luftspuren im oberen Kühlerteil an. Diese werden entfernt, indem zunächst bei geschlossenem Hahn I der Hahn D geöffnet wird. Der Apparaturteil D–I füllt sich mit Lösungsmitteldampf und Luftresten. Dann wird Hahn D geschlossen und wieder evakuiert. Das Verfahren wird wiederholt, bis das McLeod den gewünschten Entlüftungsgrad anzeigt.

Das Differentialmanometer (*b*) wird durch den Einfüllstutzen F mit der zweiten Mischungskomponente beschickt und über Schliff S mit der Entlüftungsanlage verbunden. Diese Komponente wird gleichfalls unter ihren Schmelzpunkt gekühlt und die gesamte Entlüftungsoperation nochmals wiederholt. Sodann wird die erforderliche Menge Lösungsmittel in das Vorratsgefäss V überdestilliert, wobei der Kühler E von einer Kühlsole durchflossen wird. Nach dem Abschmelzen bei H ist das Differentialmanometer messbereit.

Die gewünschten Mischungsverhältnisse werden durch Überschütteln des Lösungsmittels vom Vorratsgefäss V in das Messgefäss M hergestellt. Dieses ist graduiert und geeicht, so dass die Konzentrationen berechnet werden können.

Die Dampfdruckdifferenz zwischen Lösung und Lösungsmittel wird an der Messkapillare N abgelesen. Die Bezugsbasis für die Ablesungen ist der Flüssigkeitsmeniskus in der Kapillare Q. Diese besitzt den gleichen Querschnitt von 1,4 mm wie die Messkapillare N, so dass die Kapillaraszension keinen Einfluß auf die Ergebnisse hat*.

*Es bestanden ursprünglich Bedenken, ob nicht trotz der langen Kapillare zwischen Vorratsgefäß V für das reine Lösungsmittel und Messgefäß M mit der Lösung eine isotherme Destillation stattfinden könne. Selbst bei mehrstündiger Beobachtung konnte jedoch nach Einstellung des Gleichgewichtes nie eine Veränderung des Meniskus in der Kapillare N beobachtet werden. Eine einmal eingestellte Dampfdruckdifferenz blieb auch über Stunden hinweg konstant.

VOL. 2 1961

Die Messungen sind in einem Wasserthermostaten bei 25°C durchgeführt worden. Mit dieser Anordnung konnten die Aktivitätskoeffizienten mit einer Genauigkeit von ±2,5 Prozent bestimmt werden.

Durch graphische Intergration der Gibbs–Duhem'schen Gleichung wurden aus den gemessenen Dampfdruckerniedrigungen die Aktivitätskoeffizienten der Isomeren errechnet. Da diese zunächst auf die verdünnte Lösung bezogen sind, erfolgte eine Umnormierung auf den reinen Stoff, um weitere thermodynamische Berechnungen anschliessen zu können.

In *Tabelle 1* sind die gemessenen Dampfdruckerniedrigungen und die Aktivitätskoeffizienten der Mischsysteme Chlortoluole–Benzol zusammengestellt.

Mischungswärmen

Die Messungen sind mit einem Kalorimeter ausgeführt worden, das im Laufe verschiedener anderer Arbeiten weiterentwickelt worden ist (*Bild 2*).

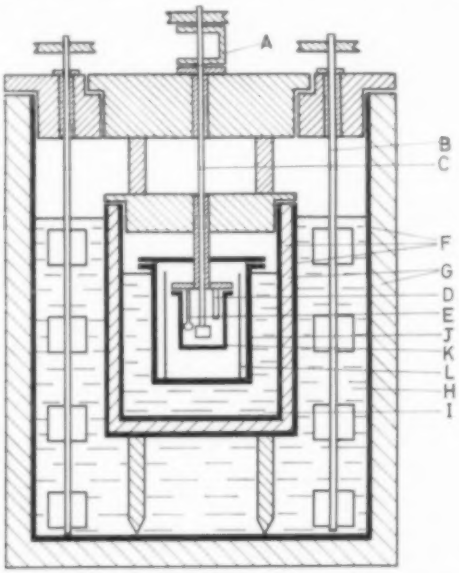

Bild 2. Schematischer Aufbau des Kalorimeters: A, Fallvorrichtung; B, Thermostatenrührer; C, Kalorimeterrührer; D, Thermosäule; E, Heizer; F, Metallgefässe; G, Isolationsschichten; H, äusseres Wasserbad, I, inneres Wasserbad; J, Mantelgefäss; K, Kalorimetergefäss; L, Konvektionsschild

Das Kalorimetergefäss besteht aus hochglanzvernickeltem Messingblech. Durch den Deckel sind der Heizer, die Thermosäule und der Rührer, der gleichzeitig als Zertrümmerer dient, gasdicht durchgeführt. Die Thermosäule besteht aus 147 Kupfer–Konstantan–Elementen. Die Ampullen sind der Form des Kalorimetergefässes weitgehend angepasst. Das Kalorimeter befindet sich in einem Tian'schen Vielmantelthermostat, dessen Temperaturschwankungen im Innenmantel kleiner als 10^{-5} Grad sind. Die gesamte Anlage ist in einem temperaturkonstanten Raum (± 0,07°) untergebracht. Die Spannung über dem elektrischen Heizer wurde mit

Tabelle 1. Aktivitätskoeffizienten der Systeme Chlortoluol–Benzol
($p^\circ_A = 94{,}91$ mm Hg; $p^\circ_B = 3{,}5 \pm 0{,}5$ mm Hg)

		o-Chlortoluol				*m-Chlortoluol*				*p-Chlortoluol*			
γ_B	p_B (mm Hg)	Δh (mm Bzl)	p_A (mm Hg)	f_A	f_B	Δh (mm Bzl)	p_A (mm Hg)	f_A	f_B	Δh (mm Bzl)	p_A (mm Hg)	f_A	f_B
0,05	0,18	72,5	90,07	0,9990	4,055	69,5	90 26	1,0011	3,848	76,0	89,85	0,9965	2,941
0,10	0,35	128,0	86,33	1,0107	3,475	125,5	86,50	1,0127	3,339	149,5	84,95	0,9946	3,060
0,15	0,53	177,0	83,01	1,0286	3,048	179,0	82,88	1,0274	3,019	209,5	80,92	1,0031	2,893
0,20	0,70	228,5	79.53	1 0476	2,788	227,0	79,62	1,0488	2,739	265,5	77,15	1,0161	2,723
0,25	0,88	276,0	76,29	1,0718	2,574	278,0	76,17	1,0701	2,558	318,5	73,56	1,0335	2,572
0,30	1,05	323,5	73,07	1,0996	2,407	324,5	73,01	1,0987	2,386	366,5	70,31	1,0583	2,419
0,35	1,23	368,0	70,03	1,1352	2,255	362,5	70,39	1,1410	2,208	407,5	67,49	1,0940	2,259
0,40	1,40	400,5	67,77	1,1901	2,085	388,5	68,54	1,2036	2,021	439,0	65,30	1,1467	2,090
0,45	1,58	424,5	66,05	1,2539	1,920	403,5	67,40	1 2796	1,847	462,5	63,61	1,2185	1,925
0,50	1,75	441,5	64,79	1,3653	1,764	415,5	66,46	1,4005	1,688	479,5	62,38	1,3146	1,771
0,55	1,93	453,5	63,84	1,4948	1,610	434,5	65,06	1,5233	1,550	494,5	61,20	1,4329	1 624
0,60	2,10	465,5	62,90	1,6569	1,507	467,0	62,80	1,6542	1,471	511,0	59,97	1,5798	1,525
0,65	2,28	479,5	61,82	1,8610	1,405	507,0	60,05	1,8077	1,395	529,5	58,60	1,7640	1,428
0,70	2,45	497,5	60,52	2,1256	1,317	550,0	57,12	2,0061	1,322	551,0	57,05	2,0036	1,343
0,75	2,63	523,0	58,67	2,4727	1,245	593,0	54,17	2,2830	1,264	576,0	55,27	2,3292	1,268
0,80	2,80	560,0	56,12	3,0046	1,182	638,5	51,08	2,6910	1,205	611,0	52,85	2,7700	1,206
0,85	2,98	615,5	52,38	3,6793	1,128	686,0	47,85	3,3611	1,150	657,0	49,71	3,4920	1,149
0,90	3,15	689,5	47,45	4,9996	1,080	736,0	44,46	4,6845	1,098	711,5	46,04	4,8510	1,098
0,95	3,33	777,0	41,65	8,7778	1,034	791,5	40,72	8,5812	1,047	772,5	41,94	8,8380	1,048

VOL
2
1961

einem Feussner-Kompensator bestimmt. Der Thermostrom ist mit einem Zeiss-Skalengalvanometer gemessen worden. Es konnten noch Temperaturänderungen von 5.10^{-5} Grad bestimmt werden. Die Messgenauigkeit liesse sich durch Kompensation des Thermostromes steigern. Das erwies sich jedoch als zwecklos, da die Hauptfehlerquelle in der Auswertung des Temperatur–Zeit–Verlaufes liegt. Eine nähere Untersuchung dieser Frage zeigte, dass bei diesen anisothermen Messungen relativ kleiner und nicht augenblicklich freiwerdender Mischungswärmen sowohl eine rechnerische wie eine graphische Auswertung des Temperaturverlaufes mit einer erheblichen Unsicherheit behaftet ist, weil $\Delta T/\Delta t$ sich nicht linear mit der Temperatur ändert. Da der Hauptanteil des mittleren Fehlers auf die Extrapolation der Temperatur–Zeit–Kurve bei der Auswertung entfällt, vergrössert er sich mit dem Betrag der Wärmetönung.

Eine Untersuchung des schon vielfach gemessenen Systems Tetrachlorkohlenstoff–Benzol zur Prüfung der Apparatur ergab gute Übereinstimmung mit den zuverlässigsten Werten anderer Autoren (*Bild 3*). Der maximale mittlere Fehler betrug bei diesen Messungen $\pm 1{,}2$ Prozent.

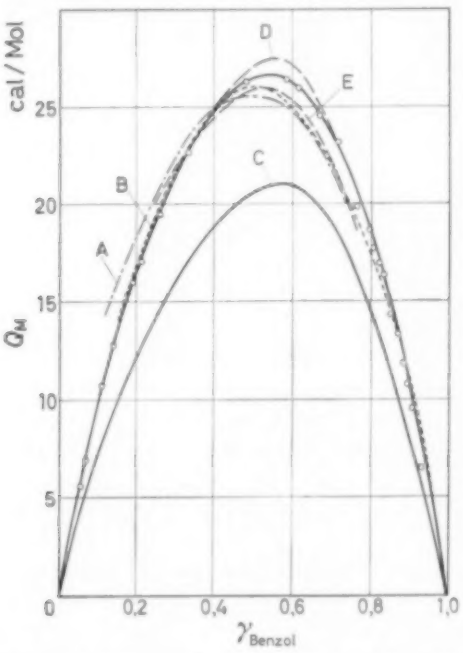

Bild 3. Mischungswärmen des Systems Tetrachlorkohlenstoff–Benzol bei 25°C in cal/Mol Mischung: A, Hirobe (1926); B, Kirejew u.a. (1937); C, Vold (1937); D, Schulze (1951); E, Cheesman u. Whitaker (1952); ○, eigene Messungen

Die mittleren molaren Mischungswärmen der drei Chlortoluole mit Benzol sind in *Tabelle 2* und *Bild 4* dargestellt. Es ist ein maximaler Fehler von $\pm 3{,}5$ Prozent berechnet worden. Während sich die

Tabelle 2. Mittlere molare Mischungswärmen der Systeme Chlortoluole–Benzol (A = Benzol; B = Chlortoluole)

γ_A	n_B (Mol)	n_A (Mol)	*Heizenergie* Q_H (cal)	*Gemessene Mischungswärme* (cal)	Q_M (cal/Mol)
			o-Chlortoluol–Benzol		
0,858	0,107	0,645	4,157	17,11	20,8
0,684	0,212	0,452	6,873	23,06	34,2
0,530	0,285	0,322	17,796	23,72	39,1
0,444	0,341	0,272	16,301	24,31	39,7
0,322	0,380	0,180	12,390	18,49	33,0
0.230	0,462	0,138	12,337	15,21	25,4
			m-Chlortoluol–Benzol		
0,950	0,031	0,582	3,460	7,52	12,2
0,842	0,113	0,601	6,951	22,68	32,0
0,749	0,167	0,497	12,462	29,95	45,2
0,575	0,253	0,342	12,439	36,10	60,6
0,446	0,356	0,287	17,810	39,15	60,8
0,401	0,363	0,243	17,894	34,45	56,8
0,311	0,416	0,188	11,689	28,01	46,4
0,203	0,451	0,115	10,860	17,12	30,3
			p-Chlortoluol–Benzol		
0,963	0,032	0,845	5,453	6.04	6,9
0,882	0,096	0,718	6,872	13,51	16,6
0,695	0,176	0,402	4,845	16,57	28,7
0,562	0,255	0,327	6,867	19,40	33,3
0,464	0,302	0,261	13,884	19,99	35,5
0,320	0,427	0,201	16,359	18,90	30,1
0,205	0,458	0,119	13,893	12,91	22,4
0,103	0,508	0,059	8,187	7,78	13,7

Mischungswärmen von *o*- und *p*-Chlortoluol im ganzen Konzentrationsbereich wenig unterschieden, ergibt das *m*-Chlortoluol fast doppelt so grosse Werte.

Mischvolumina

Die Volumina der Mischsysteme wurden aus Dichtemessungen bestimmt. Es ergab sich für alle drei Mischungen, dass im gesamten Konzentrationsbereich sich die Mischvolumina additiv aus den Einzelvolumina zusammensetzen.

THEORETISCHER TEIL

Die gemessenen Aktivitätskoeffizienten und Mischungswärmen gestatten die drei Mischsysteme der Chlortoluole mit Benzol durch ihre Überschussfunktionen zu charakterisieren. Man erhält die freie Überschussenthalpie aus

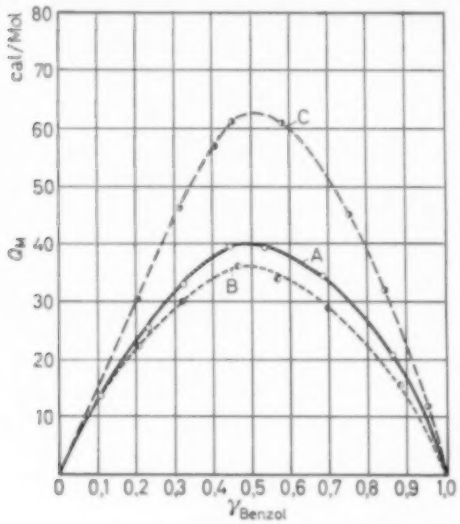

Bild 4. Mischungswärmen der Systeme Chlortoluol–Benzol bei 25°C in cal/Mol Mischung: A, *o*-Chlortoluol–Benzol; B, *m*-Chlortoluol–Benzol; C, *p*-Chlortoluol–Benzol

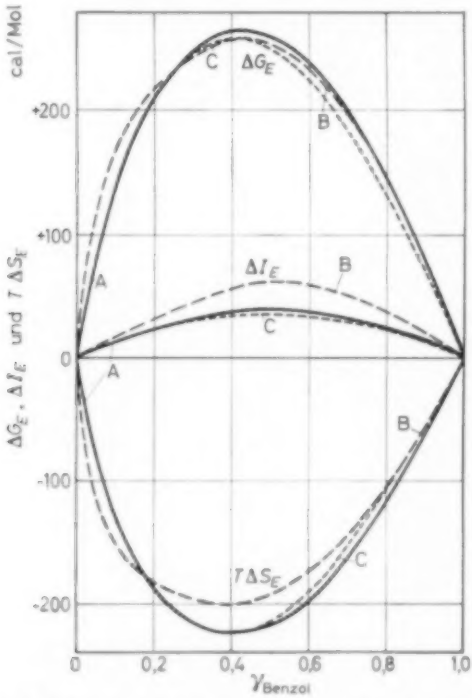

Bild 5. Überschussfunktionen der Mischsysteme Chlortoluol–Benzol bei 25°C: A, *o*-Chortoluol–Benzol; B, *m*-Chlortoluol–Benzol; C, *p*-Chlortoluol–Benzol

$$\Delta G_E = RT(\gamma_A \ln f_A + \gamma_B \ln f_B)$$

und kann nach

$$\Delta G_E = \Delta I_E - T\,\Delta S_E$$

mit den gemessenen Mischungswärmen die Überschussentropien berechnen. Diese Werte sind in *Tabelle 3* und *Bild 5* zusammengestellt.

Nach der von Guggenheim[3] aufgestellten Theorie streng regulärer Lösungen verhalten sich Mischungen, deren Partner gleiche Molekülgrösse und -gestalt besitzen, hinsichtlich ihrer Entropieänderung ideal. Für diese Systeme ist die Überschussentropie gleich Null, und es gilt

$$\Delta G_E = \Delta I_E;\ \Delta S_E = 0$$

Dieser Theorie liegt ein vereinfachtes Gittermodell zugrunde, nach dem die Moleküle der beiden Komponenten im Gitter austauschbar sind, ohne dass sich mit der Zusammensetzung die intermolekularen Abstände ändern.

Die untersuchten Mischsysteme der isomeren Chlortoluole mit Benzol gestatten keinen unmittelbaren Vergleich mit dieser Theorie, denn die Bedingung gleicher Molekülgrössen der Mischungspartner ist nicht erfüllt. Die Molvolumina (cm³/Mol) der untersuchten Stoffe sind:

Benzol	*o*-Chlortoluol	*m*-Chlortoluol	*p*-Chlortoluol
89,4 cm³/Mol	117,3 cm³/Mol	119,2 cm³/Mol	118,7 cm³/Mol

Beim Mischen wird eine Überschussentropie auftreten.

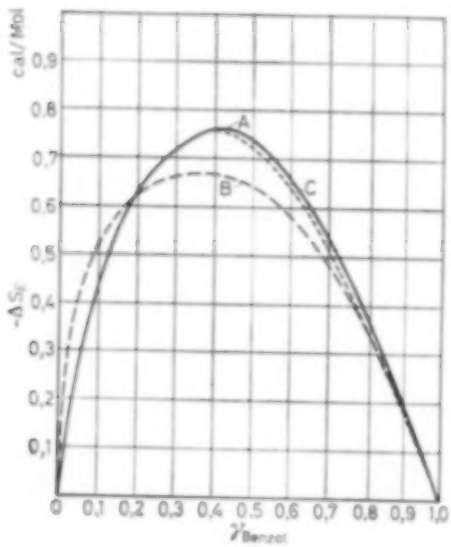

Bild 6. Überschussentropien der Mischsysteme Chlortoluol–Benzol bei 25°C: A, *o*-Chortoluol–Benzol; B, *m*-Chlortoluol–Benzol; C, *p*-Chlortoluol–Benzol

Tabelle 3. Uberschussfunktionen der Systeme Chlortoluol–Benzol

γ_B	*o-Chlortoluol*				*m-Chlortoluol*				*p-Chlortoluol–Benzol*			
	ΔG_E (cal/Mol)	ΔI_E (cal/Mol)	$T\Delta S_E$ (cal/Mol)	ΔS_E (Cl/Mol)	ΔG_E (cal/Mol)	ΔI_E (cal/Mol)	$T\Delta S_E$ (cal/Mol)	ΔS_E (Cl/Mol)	ΔG_E (cal/Mol)	ΔI_E (cal/Mol)	$T\Delta S_E$ (cal/Mol)	ΔS_E (Cl/Mol)
0,05	40,9	8,4	− 32,5	−0,11	40,58	12,2	− 32,4	−0,11	30,0	7,2	− 22,8	−0,08
0,10	74,4	15,4	− 59,0	−0,20	78,15	21,7	− 56,5	−0,19	63,4	13,4	− 50,0	−0,17
0,15	113,4	21,3	− 92,1	−0,31	111,8	30,4	− 81,4	−0,27	96,5	18,1	− 78,4	−0,26
0,20	143,5	26,3	−117,2	−0,38	142,4	38,4	−104,0	−0,35	128,0	22,0	−106,0	−p,36
0,25	170,8	30,4	−140,4	−0,47	169,2	45,3	−123,9	−0,42	154,6	25,7	−128,9	−0,43
0,30	195,6	33,6	−162,0	−0,54	193,6	51,0	−142,6	−0,48	180,5	28,7	−151,8	−0,51
0,35	217,3	36,0	−181,3	−0,61	215,1	55,8	−159,3	−0,53	202,6	31,0	−171,6	−0,58
0,40	236,0	37,8	−198,2	−0,66	232,6	59,3	−173,3	−0,58	223,4	32,5	−190,9	−0,64
0,45	247,4	39,0	−208,4	−0,70	244,7	60,8	−183,9	−0,62	239,1	34,1	−205,0	−0,69
0,50	260,3	39,8	−220,5	−0,74	254,8	62,2	−192,6	−0,65	250,4	35,3	−215,1	−0,72
0,55	262,5	39,9	−222,6	−0,75	254,9	61,0	−193,9	−0,65	253,9	35,3	−218,6	−0,73
0,60	265,4	38,1	−227,3	−0,76	256,5	57,0	−199,5	−0,67	258,5	34,2	−224,3	−0,76
0,65	259,6	35,3	−224,3	−0,75	251,0	51,3	−199,6	−0,67	254,8	32,1	−222,7	−0,75
0,70	248,4	31,5	−216,9	−0,73	241,0	45,2	−195,8	−0,66	245,5	29,5	−216,0	−0,72
0,75	231,3	27,3	−204,0	−0,68	226,3	38,2	−188,1	−0,63	230,8	25,9	−204,9	−0,69
0,80	207,5	22,5	−185,0	−0,62	211,1	30,1	−181,0	−0,61	209,7	21,8	−187,9	−0,63
0,85	176,6	17,3	−159,3	−0,53	199,3	23,7	−175,6	−0,59	181,1	17,9	−163,2	−0,55
0,90	136,5	11,9	−124,6	−0,42	173,9	15,9	−158,0	−0,53	143,4	13,3	−130,1	−0,44
0,95	83,1	5,9	− 77,2	−0,26	124,2	8,1	−116,1	−0,39	90,8	7,2	− 83,6	−0,28

Wenn jedoch das Guggenheim'sche Modell die tatsächlichen Mischungsvorgänge wiederzugeben vermag, so ist zu erwarten, dass die Überschussentropien der drei Mischsysteme gleich oder doch zumindest ähnlich sind. Denn die Molekülgrössen der drei Isomeren unterscheiden sich kaum, so dass das Grössenverhältnis zwischen den Mischungskomponenten stets gleich ist. Bei Austausch der Molekülarten wäre stets eine gleiche Änderung des Gittertypes zu erwarten.

Ein Vergleich der in *Tabelle 3* bzw. in *Bild 6* wiedergegebenen Überschussentropien ergibt tatsächlich, dass sich die Werte für die drei Isomeren nicht wesentlich unterscheiden. Über die zweifellos vorhandenen Unterschiede, vor allem die grösseren Abweichungen bei der *m*-Verbindung, lässt sich allein auf Grund thermochemischer Messungen nichts aussagen. Diese Ergebnisse zeigen, dass die Guggenheim'sche Theorie zumindest im Sinne eines vereinfachenden Modelles das Verhalten der Mischungen zu beschreiben gestattet.

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VOL
2
1961

ÉTUDE THERMODYNAMIQUE DES RÉACTIONS DE DOUBLE DECOMPOSITION EN PHASES SOLIDES

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GÉNÉRALITÉS SUR LES ÉQUILIBRES CHIMIQUES Á L'ÉTAT SOLIDE

Malgré le nombre élevé de réactions à l'état solide étudiées jusqu'à ce jour, très peu d'équilibres chimiques ont été mis en évidence.

En 1885, Spring[1] crut démontrer par analyse chimique l'existence de l'équilibre:

$$BaSO_4 + Na_2CO_3 = BaCO_3 + Na_2SO_4$$

à température ambiante et sous une pression de 6000 atm. De nombreux auteurs[2–4] contestèrent par la suite les résultats de Spring, sans cependant refaire ses expériences.

Plus tard, en 1929, Tubandt et Reinhold[5] étudièrent les équilibres suivants à 200°C par la " méthode des pastilles ":

$$2\,AgI + Cu_2S = 2\,CuI + Ag_2S$$

$$Ag_2Se + Cu_2S = Cu_2Se + Ag_2S$$

Enfin en 1940, Wood et ses collaborateurs[6] mirent en évidence, par étude aux rayons X, l'équilibre:

$$KBr + CsCl = KCl + CsBr$$

obtenu à 400°C.

Ce bref rappel historique montre que le nombre de travaux effectués dans ce domaine est fort restreint.

Examinons les conditions indispensables à la mise en évidence de tels équilibres:

Tout d'abord, pour que l'équilibre soit thermodynamiquement possible, il faut qu'au minimum deux des corps intervenant dans la réaction soient miscibles en toute proportion. L'existence d'une solution solide rend alors le système bivariant.

La valeur absolue de l'enthalpie libre de réaction doit être faible (< 10 kcal), car autrement la mise en évidence d'une constante d'équilibre trop forte ou trop faible nécessiterait le dosage de traces de réaction.

Or le problème du dosage des réactions à l'état solide est particulièrement délicat puisqu'on risque d'altérer la composition du mélange au cours du dosage.

L'analyse aux rayons X devrait être la méthode d'élection. En fait, la faible quantité de l'échantillon analysé, le grand nombre de raies obtenues rendent difficile une interprétation quantitative acceptable.

La " méthode des pastilles " employée par Tubandt et Reinhold semble très précise, mais n'est applicable que dans des cas très particuliers.

Il reste enfin l'analyse chimique par voie humide, dont l'emploi est lié à l'existence d'un solvant sélectif.

Si l'on ajoute aux difficultés qui viennent d'être énumérées que les réactions entre solides sont lentes, c'est-à-dire que la durée d'obtention d'un équilibre peut varier, suivant les conditions, de quelques heures à des mois, le faible nombre de résultats obtenus dans ce domaine devient explicable.

Nous étudierons successivement les résultats obtenus pour:

2 systèmes bivariants;

1 système univariant.

VOL. 2 1961

ÉTUDE DE L'ÉQUILIBRE

$$BaSO_4 + Na_2CO_3 = BaCO_3 + Na_2SO_4$$

Cet équilibre fut étudié par Spring, mais il a été dit plus haut que les résultats de cet auteur furent souvent contestés.

Après la mise au point d'une méthode de dosage convenable[7], basée sur la dissolution sélective de Na_2SO_4 et Na_2CO_3 par une solution aqueuse à 10 pour cent de carbonate d'ammonium, les expériences de Spring furent refaites.

Aucune trace de réaction n'a été observée à température ambiante, même sous une pression de 14000 atm. Les résultats de Spring ne peuvent donc s'expliquer que par l'intervention d'une réaction au cours du dosage.

Vu la faible valeur de l'enthalpie libre de réaction calculable à partir des tables de constantes[8],

$$BaSO_4 + Na_2CO_3 = BaCO_3 + Na_2SO_4;\ \Delta G^\circ_{298^\circ K} \simeq -1 \text{ à } -2 \text{ kcal}$$

et l'existence d'une solution solide $Na_2(CO_3,SO_4)$ en toute proportion à haute température[9-12], nous avons pensé que l'équilibre était possible à haute température.

Les expériences furent ainsi menées: deux grammes de mélange poudreux étaient introduits dans un creuset de platine et portés à la température désirée. En cours d'expérience, les mélanges étaient plusieurs fois sortis du four pour être broyés au mortier afin de renouveler les surfaces de contact. La durée de l'obtention de l'équilibre variait de quelques heures à deux mois suivant la nature des mélanges et la température de l'expérience. Cet équilibre était déterminé par la limite commune de deux réactions inverses.

Deux séries d'expériences ont d'abord été faites à 700°C, la première sur les mélanges de composition initiale:

$$BaSO_4 + A\ Na_2CO_3$$

la seconde sur les mélanges:

$$BaCO_3 + B\ Na_2SO_4$$

A et B étant compris entre 0 et 5.

Étude de la réaction $BaSO_4 + A\ Na_2CO_3$ à 700°C

L'équilibre a été mis en évidence au moyen de deux mélanges inverses:

$$BaSO_4 + A\ Na_2CO_3 \text{ et } BaCO_3 + Na_2SO_4 + (A-1)Na_2CO_3$$

Soit ρ le rapport du nombre de moles $BaCO_3$ à l'équilibre au nombre total d'ions SO_4^{2-} de mélange, si l'on suppose qu'il se forme seulement la solution solide $Na_2(CO_3,SO_4)$ et que celle-ci est parfaite, la constante d'équilibre relative aux fractions molaires s'exprime par:

$$K_x = \frac{x_{Na_2SO_4}}{x_{Na_2CO_3}} = \frac{\rho}{A-\rho} = K$$

soit

$$\rho = \frac{K}{K+1} A$$

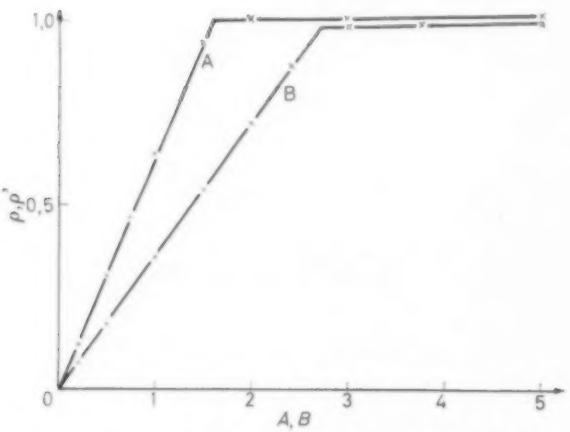

Figure 1. A, $BaSO_4 + A\ Na_2CO_3$ à 700°C; B, $BaCO_3 + B\ Na_2SO_4$ à 700°C

Donc ρ doit varier linéairement avec A. La courbe A de la *Figure 1* représente la courbe expérimentale $\rho = f(A)$. Cette courbe est une droite jusqu'à $A = 1{,}6$ environ. La mesure de la pente de cette droite a donné:

$$K = 1{,}70$$

Étude de la réaction $BaCO_3 + B\,Na_2SO_4$ à 700°C

Les deux mélanges inverses ont été étudiés:

$$BaCO_3 + B\,Na_2SO_4 \quad \text{et} \quad BaSO_4 + Na_2CO_3 + (B-1)Na_2SO_4$$

Appelons ρ' le rapport du nombre de moles de $BaSO_4$ à l'équilibre au nombre d'ions CO_3^{2-} total dans le mélange.

On peut montrer facilement que:

$$\rho' = \frac{1}{K+1}\,B$$

Effectivement la courbe B de la *Figure 1* montre que les points expérimentaux s'alignent jusqu'à $B = 2{,}6$ environ, suivant une droite dont le coefficient angulaire a donné:

$$K = 1{,}76$$

Interpretation des résultats

Par deux séries de mélanges de compositions différentes, nous avons trouvé pour la constante d'équilibre:

$$K = 1{,}70$$

$$K = 1{,}76$$

soit $$K = 1{,}73 \pm 0{,}03$$

Par conséquent les points de la courbe A caractérisée par:

$$\rho = \frac{K}{K+1}\,A = \frac{1{,}73}{1+1{,}73}\,A = \frac{1}{1{,}58}\,A \quad \text{et} \quad 0 < \rho \leqslant 1$$

doivent être alignés jusqu'à $A = 1{,}58$, mais pour $A \geqslant 1{,}58$, ρ ne peut être égal qu'à l'unité. Effectivement, pour $A = 2, 3, 5$, la réaction a été complète.

De même, à partir de $B = 2{,}73$, la réaction doit être complète. En fait, des difficultés de dosage n'ont pas permis de déterminer ρ' avec précision. Des expériences sont actuellement en cours pour résoudre cette difficulté.

Calcul de l'enthalpie de réaction

Si l'on suppose la solution solide parfaite, l'enthalpie libre de réaction est liée à K par la formule:

$$\Delta G^\circ = -RT \log_e K$$

A 700°C, $K = 1{,}73 \pm 0{,}03$, d'où $\Delta G^\circ_{700^\circ C} = -(1065 \pm 34)$ cal

Le calcul à partir des tables[8] de l'enthalpie libre de formation donne:

$$\Delta G^\circ_{25^\circ C} = -1200 \text{ cal}$$

VOL. 2 1961

Les résultats expérimentaux sont donc en bon accord avec les résultats obtenus par le calcul puisqu'on peut admettre[7] que ΔG° d'une réaction à l'état solide varie peu avec la température et surtout que l'imprécision sur la valeur de ΔG° calculée à partir des tables s'élève à quelques kilocalories.

Des expériences plus sommaires ont été faites sur les mélanges équimoléculaires à 600°C et 500°C:

$$\text{à } 600°C \quad K = 1{,}95$$

$$\text{à } 500°C \quad K = 1{,}98$$

La faible valeur de l'enthalpie de réaction, $\Delta H^\circ_{25°C} = -1{,}7$ kcal, calculable à partir des tables explique parfaitement la faible variation de K avec la température.

ÉTUDE DE L'ÉQUILIBRE

$$\mathbf{BaSO_4 + K_2CO_3 = BaCO_3 + K_2SO_4}$$

L'existence d'une solution solide $K_2(SO_4,CO_3)$ à haute température[10] permettant la formation d'un équilibre, cette réaction a été étudiée par la même technique expérimentale que celle décrite précédemment.

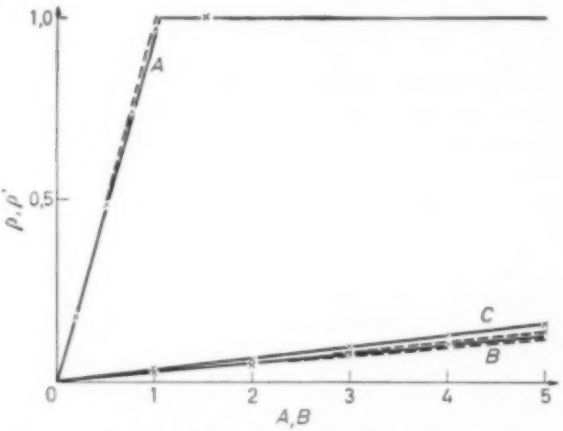

Figure 2. A, $BaSO_4 + A\ K_2CO_3$ à 650°C; B, $BaCO_3 + B\ K_2SO_4$ à 650°C; C, $BaCO_3 + B\ K_2SO_4$ à 700°C

Équilibre à 650°C

La droite A de la *Figure 2* rend compte des résultats obtenus au moyen des mélanges:

$$BaSO_4 + A\ K_2CO_3 \quad \text{et} \quad BaCO_3 + K_2SO_4 + (A-1)K_2CO_3$$

Le coefficient angulaire de la droite A permet de calculer:

$$K_1 = 50$$

La droite B de la même figure a été obtenue avec les mélanges:

$$BaCO_3 + B\,K_2SO_4 \quad \text{et} \quad BaSO_4 + K_2CO_3 + (B-1)K_2SO_4$$

Son coefficient angulaire a donné:

$$K_2 = 36{,}0$$

En fait, la constante K_1 déterminée à partir de la droite A est très imprécise puisque un très faible changement de pente de cette droite entraine une grande variation sur K_1; ainsi la droite représentée en tirets qui est presque confondue avec la droite A correspondrait à une constante $K_1' = \infty$.

Par contre, les deux droites en tirets contenant la droite B ont donné:

$$K_2 = 36 \pm 3$$

C'est donc cette dernière valeur que nous adopterons pour la constante d'équilibre à 650°C:

$$K_{650°} = 36 \pm 3$$

Équilibre à 700°C

La courbe C a été obtenue avec les mélanges (B). La pente de la droite donne*:

$$K_{700°} = 29 \pm 2$$

Calcul des fonctions thermodynamiques

Si l'on suppose la solution solide $K_2(CO_3,SO_4)$ parfaite, on peut calculer l'enthalpie libre de réaction à partir des constantes d'équilibres déterminées expérimentalement:

$$\Delta G^\circ_{650°C} = -(6610 \pm 160)\ \text{cal}$$

$$\Delta G^\circ_{700°C} = -(6470 \pm 140)\ \text{cal}$$

L'absence de données sur le carbonate de potassium ne permet pas le calcul de ΔG° à partir des tables, par contre on peut vérifier que, comme pour la plupart des réactions à l'état solide[7]:

$$\Delta G^\circ_T \simeq \Delta G^\circ_{25°C} \simeq \Delta H^\circ_{25°C}$$

En effet, à partir des tables, on obtient:

$$\Delta H^\circ_{25°C} = -9800\ \text{cal}$$

On obtient aussi le même ordre de grandeur en calculant ΔH° à partir de $K_{650°C}$ et $K_{700°C}$ au moyen de la formule:

$$\frac{\partial \log K}{\partial T} = \frac{\Delta H^\circ}{RT^2}$$

qui donne $$\Delta H^\circ = -9000\ \text{cal}$$

* Dans un mémoire antérieur (*Compt. rend.* **247**, 451 (1958)) la valeur $K = 28 \pm 2$ a été donnée. La valeur $K = 29 \pm 2$ semble meilleure.

VOL. 2 1961

ÉTUDE DE LA RÉACTION

$$BaCO_3 + Li_2SO_4 = BaSO_4 + Li_2CO_3$$

L'absence de solution solide $Li_2(CO_3,SO_4)$ est connue déjà depuis fort longtemps[10]. Le calcul de l'enthalpie de réaction* à partir des tables donne:

$$BaCO_3 + Li_2SO_4 = BaSO_4 + Li_2CO_3;\ \Delta H^\circ_{25^\circ C} = -6{,}61 \text{ kcal}$$

Par conséquent, contrairement aux réactions précédemment étudiées avec le sodium et le potassium, cette réaction:

–doit se faire dans le sens de la formation du sulfate de baryum, car $\Delta G^\circ \simeq \Delta H^\circ < 0$;

–doit se faire complètement puisque le mélange des quatre sels constitue un système univariant.

Afin de vérifier ces résultats, divers mélanges ont été étudiés à 530°C (la température de fusion la plus basse est 540°).

Les mélanges $BaSO_4 + A\ Li_2CO_3$ n'ont donné aucune trace de réaction au bout de quinze jours. Par contre, les mélanges $BaCO_3 + B\ Li_2SO_4$ ont réagi entièrement dans les mêmes conditions. Ces expériences confirment donc que le système constitué par les quatre sels $BaSO_4$, $BaCO_3$, Li_2SO_4, Li_2CO_3 est bien un systéme univariant.

CONCLUSION

Il ressort de l'étude précédente que des équilibres thermodynamiques peuvent être obtenus à l'état solide.

La détermination de la constante de ces équilibres permet d'atteindre les fonctions d'état de la transformation. Les valeurs ainsi déterminées et celles obtenues par d'autres voies et rassemblées dans des tables sont suffisamment voisines pour qu'on puisse admettre que les grandeurs d'excès de ces transformations sont négligeables et qu'en conséquence les systèmes en réaction se comportent sensiblement comme des systèmes parfaits. Des études en cours confirment encore ce point de vue.

Enfin, l'étude des réactions à l'état solide permet de détecter l'existence de solutions solides.

Ainsi les résultats obtenus pour les réactions:

$$BaSO_4 + Na_2CO_3 = BaCO_3 + Na_2SO_4$$

$$BaSO_4 + K_2CO_3 = BaCO_3 + K_2SO_4$$

permettent d'affirmer que dans chaque cas il n'y a qu'une seule solution solide formée, respectivement:

$$Na_2(CO_3,SO_4) \quad \text{et} \quad K_2(CO_3,SO_4)$$

Par contre, au cours de la réaction:

$$BaCO_3 + Li_2SO_4 = BaSO_4 + Li_2CO_3$$

il n'y a pas formation de solution solide.

* L'enthalpie libre ne peut être calculée à cause du manque de données sur le sulfate de lithium.

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VOL.
2
1961

ÉTUDE THERMODYNAMIQUE D'UN HALOGÉNURE MIXTE DE CUIVRE

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INTRODUCTION

Les halogénures mixtes, de formule générale MX_mY_n, où X et Y désignent deux atomes d'halogènes différents, appartiennent à une classe de corps dont l'étude des propriétés ne semble pas, à quelques exceptions près, avoir été abordée jusqu'ici. Un certain nombre d'entre eux ont bien été signalés, le plus souvent en solution, mais leur existence, à l'état cristallisé, semble parfois douteuse encore. Seuls, quelques halogénures mixtes de fer(III) et de chrome(III) ont été étudiés, et leurs propriétés thermodynamiques, leurs tensions de dissociation et leur structure cristalline sont connus.

Les auteurs de ces travaux n'ont étudié que quelques composés mixtes particuliers, et ne semblent pas s'être intéressés au problème de la prévision générale d'existence de ces corps. En se basant sur les résultats acquis pour les quelques halogénures mixtes étudiés, nous proposons une méthode qui permet de prévoir l'existence de tels composés d'un métal, par une évaluation de leurs propriétés thermodynamiques normales à 25°, à partir des valeurs, en général connues, des propriétés thermodynamiques normales des halogénures simples.

Cette méthode est appliquée au cas des halogénures mixtes de cuivre; et, dans le cas du chlorobromure cuivrique, les valeurs calculées des grandeurs thermodynamiques seront comparées aux valeurs expérimentales.

PRÉVISION DE LA STABILITÉ DES HALOGÉNURES MIXTES

Cas des halogénures mixtes de fer(III) et de chrome(III)

Quelques halogénures mixtes métalliques sont connus depuis longtemps: dès 1893, Lenormand[1] signalait avoir obtenu le chlorobromure de fer $FeCl_2Br$, stable à la température ambiante et cristallisé en larges plaquettes hexagonales. L'étude de tels composés n'a été reprise que ces dernières années; et les valeurs thermodynamiques n'ont été données, semble-t-il, que pour le chlorobromure de fer $FeCl_2Br$ et les chloroiodure et bromoiodure de chrome $CrCl_2I$ et $CrBr_2I$ (*Tableaux 1* et *2*).

Dans la série des halogénures mixtes du fer et du chrome, seuls sont connus les composés suivants: $FeCl_2Br$, $CrCl_2Br$, $CrCl_2I$ et $CrBr_2I$. D'autres composés peuvent-ils cependant exister?

De tels halogénures seront stables si, dans leur réaction de formation à partir d'un halogénure et d'un halogène,

$$MX_2 + \tfrac{1}{2}\,Y_2 \rightleftharpoons MX_2Y$$

l'enthalpie libre normale de formation MX_2Y est inférieure à l'enthalpie

Tableau 1. Constantes thermodynamiques normales des halogénures de fer

Phase solide	*Ref.*	H° (kcal/mole)	G° (kcal/mole)	S° (u.e.)
FeF_2	2	− 168	− 157,6	20
	3			20,79
$FeCl_2$	4	− 81,5	− 72,2	28,6
	2	− 81,9	− 72,2	28,7
	5	− 81,5		
	6	− 81,8		
$FeBr_2$	4	− 60		
	2	− 67,3	− 57,5	32
	5	− 58,7		
FeI_2	3	− 30		
	2	− 45	− 35,2	36
FeF_3	2	− 235	− 219	25
$FeCl_3$	4	− 96,8		
	2	− 96	− 82	39
	7	− 93,5	− 78,6	36,9
	5	− 93,4		
	6	− 95,7		
$FeBr_3$	2	− 76	− 61,6	46
	8	− 75	− 59	42
	5	− 62,8		
$FeCl_2Br$	9	− 87	− 73	43
	5	− 82,9		

Tableau 2. Constantes thermodynamiques normales des halogénures de chrome

Phase solide	*Ref.*	H° (kcal/mole)	G° (kcal/mole)	S° (u.e.)
CrF_2	4	− 181		
	2	− 182	− 172	20
$CrCl_2$	4	− 94,5	− 85	21,4
	2, 10	− 97	− 88	27,7
	11	− 95,6		
	12	− 93,9		
	13	− 92,75		
$CrBr_2$	2	− 81	− 71	− 30
	14	− 87		
CrI_2	4	− 54,2		
	2	− 58	− 48	34
	15	− 37,8		
	16	− 31		
CrF_3	2, 4	− 266	− 250	25
$CrCl_3$	4, 10	− 134,6	− 118	30
		− 132	− 115	30
$CrBr_3$	2	− 102	− 87	44
	14	− 110		
CrI_3	15	− 44,2	− 47	49
	17	− 47,8		
$CrCl_2I$	16	− 108		
$CrBr_2I$	16	− 88		

VOL. 2 1961

libre normale de formation de MX_2. Les enthalpies libres normales molaires de formation de ces divers composés solides hypothétiques peuvent être approximativement évaluées. La relation:

$$\Delta G^\circ(MX_2Y) = \Delta H^\circ(MX_2Y) - 298{,}1\,[S^\circ(MX_2Y) - S^\circ(M) - S^\circ(X_2) - \tfrac{1}{2}\,S^\circ(Y_2)] \qquad (1)$$

relie l'enthalpie libre normale de formation du composé MX_2Y à 25°, à l'enthalpie normale de formation ΔH° et aux entropies absolues S° (toutes ces quantités se rapportant aux substances prises dans l'état de référence: $P = 1$ atm, $T = 298$°K). La connaissance des données enthalpiques et entropiques permettra l'évaluation de l'enthalpie libre normale du composé MX_2Y considéré.

L'enthalpie normale de formation peut être reliée à des données que l'on connait ou que l'on peut essayer d'évaluer au moyen du cycle de Born–Haber mis sous la forme simplifiée:

$$\Delta H^\circ(MX_2Y) = H^\circ(M^{3+}{}_{(g.)}) + 2H^\circ(X^-{}_{(g.)}) + H^\circ(Y^-{}_{(g.)}) - U \qquad (2)$$

où U est l'énergie de réseau du composé MX_2Y considéré. Pour les composés étudiés, de la série du chrome et du fer, seules manquent les énergies de réseau. Les autres valeurs sont connues.

Les méthodes proposées pour le calcul direct de l'énergie de réseau ne sont pas applicables dans le cas présent: le calcul suppose que les cristaux

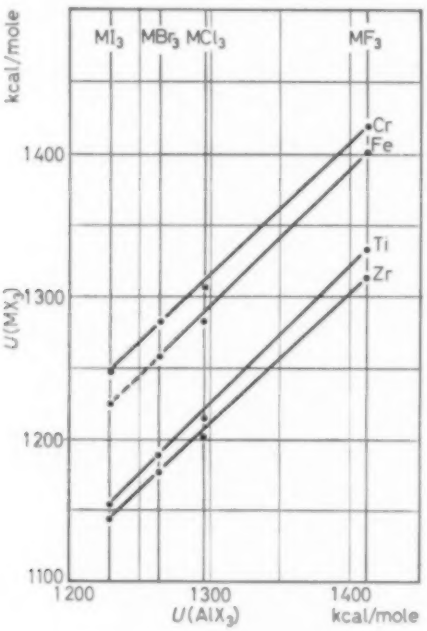

Figure 1

sont ioniques, ce qui n'est vrai, approximativement, que pour les métaux alcalins et alcalino-terreux. La méthode graphique proposée par Karapet'yants[18] qui a montré l'existence de relations linéaires entre les énergies de réseau expérimentales de séries homologues d'halogénures simples, peut permettre, par extrapolation, la détermination d'énergies de réseau inconnues: l'énergie de réseau de FeI_3 peut être évaluée de cette manière (*Figure 1*); on pourra donc tracer la droite caractéristique du couple considéré halogénures de fer(III)–halogénures de chrome(III) (*Figure 2*).

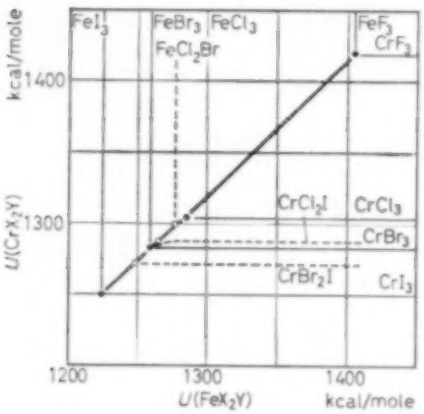

Figure 2

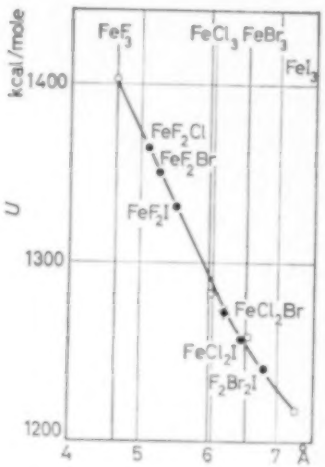

Figure 3

$FeCl_2Br$ possède une structure cristalline semblable à celle des chlorure et bromure ferriques[9]. Il en est de même pour les halogénures mixtes de chrome(III) dont les paramètres cristallins s'intercalent dans la série des paramètres cristallins des trihalogénures[19]. Il parait donc valable de supposer que les points représentatifs des halogénures mixtes vont se placer sur la droite caractéristique du couple considéré, halogénures de fer(III), halogénures de chrome(III), d'autant plus que leurs structures sont presque équivalentes à celles de solutions solides idéales de MX_3 et MY_3. Cette méthode est toutefois de portée limitée dans le cas présent, les données utilisables pour les halogénures mixtes étant trop peu nombreuses.

Une autre méthode paraît plus fructueuse. En portant en ordonnée les énergies de réseau des quatre halogénures simples d'un métal, et en abscisse la somme des rayons ioniques cristallins [21–24], il a été observé[2(a), 18] que les points obtenus pour les fluorure, chlorure et bromure se placent sur une droite de pente négative, le point obtenu pour l'iodure se place quelque peu au dessus de cette droite, mais il est toujours possible de tracer une courbe passant sur ces quatre points (*Figures 3* et *4*): une telle courbe est caractéristique de la série des divers halogénures du métal considéré. On peut émettre l'hypothèse que, d'une façon générale les points représentatifs des halogénures mixtes seront également situés sur cette courbe; cette hypothèse est justifiée, puisque les points correspondant aux corps connus,

à $FeCl_2Br$ (*Figure 3*) comme à $CrCl_2I$ et $ClBr_2I$ (*Figure 4*) se placent correctement sur les courbes considérées. Comme les rayons ioniques cristallins sont connus (*Tableau 3*) les énergies de réseau des halogénures mixtes inconnus et hypothètiques pourront se déduire des courbes précédentes; de plus, les points correspondant aux valeurs trouvées par cette méthode se placent correctement sur la droite caractéristique du couple halogènure de fer(III)–halogènure de chrome(III) (*Figure 5*).

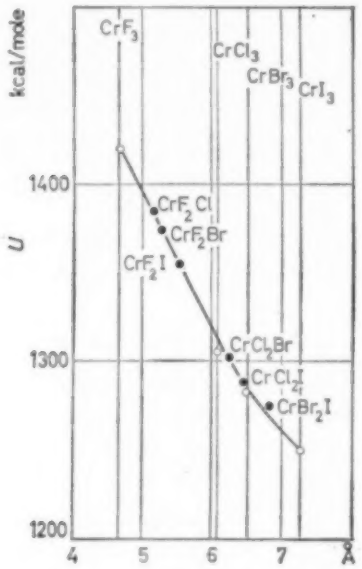

Figure 4

Tableau 3. Rayons des ions cristallins

	F^-	Cl^-	Br^-	I^-	Fe^{3+}	Cr^{3+}	Cu^{2+}
Rayons ioniques (Å)	1,34	1,81	1,96	2,20	0,65	0,62	0,72

Les valeurs trouvées pour les énergies de réseau et les enthalpies normales de formation qui s'en déduisent, sont rassemblées dans les *Tableaux 4* et *5*.

Pour calculer l'enthalpie libre normale à partir de l'équation (1), il convient de connaître les diverses entropies absolues; ces valeurs sont estimées par la méthode de Latimer[20] qui, bien qu'approchée, permet du moins une précision supérieure à celle que peuvent fournir les autres formules de secours.

Les variations des enthalpies libres normales ΔG° des réactions de formation des halogénures mixtes de fer(III) et de chrome(III) sont

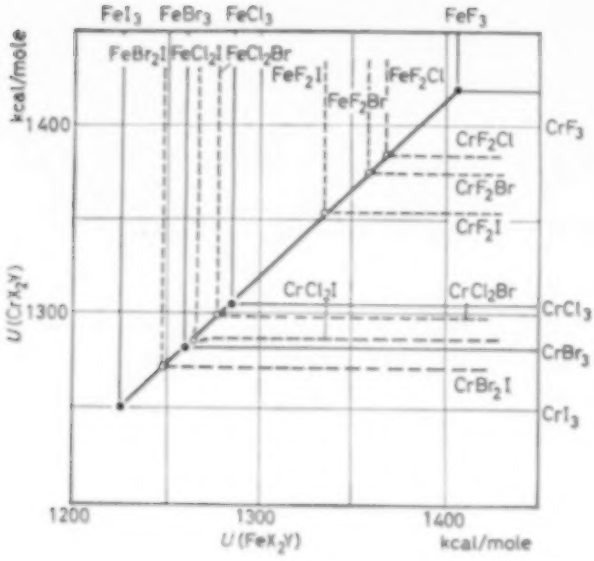

Figure 5

Tableau 4. Constantes thermodynamiques normales des halogénures de fer(III)

	U (kcal/mole)	$\Delta H^\circ(FeX_2Y_{(c.)})$ (kcal/mole)	$S^\circ(FeX_2Y_{(c.)})$ (u.e.)	$\Delta G^\circ(FeX_2Y)$ (kcal/mole)
FeF_3	1403	− 235	25	− 219
$FeCl_3$	1282	− 95	36,9	− 80
$FeBr_3$	1259	− 63	42	− 60
FeI_3	1223	− 6	47,9	− 6
FeF_2Cl	1365	− 190	25,3	− 173
FeF_2Br	1351	− 173	27,4	− 159
FeF_2I	1331	− 146	30,9	− 133
$FeCl_2Br$	1276	− 86	33,2	− 73
$FeCl_2I$	1260	− 63	36,7	− 52
$FeBr_2I$	1245	− 40	40,9	− 34

Tableau 5. Constantes thermodynamiques normales des halogénures de chrome(III)

	U (kcal/mole)	$\Delta H^\circ(CrX_2Y_{(c.)})$ (kcal/mole)	$S^\circ(CrX_2Y_{(c.)})$ (u.e.)	$\Delta G^\circ(CrX_2Y_{(c.)})$ (kcal/mole)
CrF_3	1420	− 266	25	− 250
$CrCl_3$	1306	− 134	30	− 118
$CrBr_3$	1283	− 102	44	− 87
CrI_3	1250	− 47	49	− 47
CrF_2Cl	1385	− 225	25,1	− 208
CrF_2Br	1375	− 212	27,2	− 198
CrF_2I	1355	− 185	30,7	− 174
$CrCl_2Br$	1302	− 126	33,0	− 113
$CrCl_2I$	1286	− 108	36,5	− 94
$CrBr_2I$	1274	− 86	40,7	− 78

rassemblées dans les *Tableaux 6* et *7*, ainsi que les valeurs précédemment obtenues pour les trihalogénures.

Si tous les halogénures de chrome hypothétiques peuvent être considérés comme stables, il n'en est pas de même des halogénures de fer: outre l'iodure ferrique que l'on savait déjà être instable—et les résultats le confirment—aucun des halogénures mixtes supposés, contenant de l'iode,

Tableau 6. Enthalpies libres normales des réactions de formation des halogénures de fer(III)

	$\Delta G°$(kcal/mole)
$FeF_{3(c.)} + \frac{1}{2} F_{2(g.)} \rightleftarrows FeF_{5(c.)}$	− 62
$FeCl_{3(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows FeCl_{5(c.)}$	− 8
$FeBr_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows FeBr_{5(c.)}$	− 3
$FeI_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows FeI_{5(c.)}$	+ 29
$FeF_{3(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows FeF_3Cl_{(c.)}$	− 16
$FeF_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows FeF_3Br_{(c.)}$	− 2
$FeF_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows FeF_3I_{(c.)}$	+ 29
$FeCl_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows FeCl_3Br_{(c.)}$	− 1 (− 0,8)
$FeCl_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows FeCl_3I_{(c.)}$	+ 20
$FeBr_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows FeBr_3I_{(c.)}$	+ 23

Tableau 7. Enthalpies libres normales des réactions de formation des halogénures de chrome(III)

	$\Delta G°$(kcal/mole)
$CrF_{3(c.)} + \frac{1}{2} F_{2(g.)} \rightleftarrows CrF_{5(c.)}$	− 78
$CrCl_{3(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows CrCl_{5(c.)}$	− 30
$CrBr_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CrBr_{5(c.)}$	− 16
$CrI_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CrI_{5(c.)}$	− 11
$CrF_{3(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows CrF_3Cl_{(c.)}$	− 36
$CrF_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CrF_3Br_{(c.)}$	− 26
$CrF_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CrF_3I_{(c.)}$	− 2
$CrCl_{3(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CrCl_3Br_{(c.)}$	− 25
$CrCl_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CrCl_3I_{(c.)}$	− 6
$CrBr_{3(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CrBr_3I_{(c.)}$	− 7

n'est stable; par contre, les trois autres halogénures mixtes peuvent être considérés comme suffisamment stables pour qu'il soit permis d'espérer les obtenir cristallisés.

Application aux halogénures mixtes de cuivre

Cette méthode de calcul des énergies de réseau peut être étendue à d'autres séries d'halogénures métalliques, et permet, en particulier, le calcul des énergies de réseau et par suite, celui des enthalpies libres normales des halogénures mixtes de cuivre(II). On utilise la courbe caractéristique de cette série d'halogénures (*Figure 6*), construite à partir des énergies de réseau[25, 26] et de la somme des rayons ioniques des halogénures simples. On en déduit l'enthalpie de formation de ces composés (équation 2) et, connaissant les valeurs des entropies normales[20], on peut évaluer leur énergie libre normale de formation (*Tableau 8*). Les variations d'enthalpie

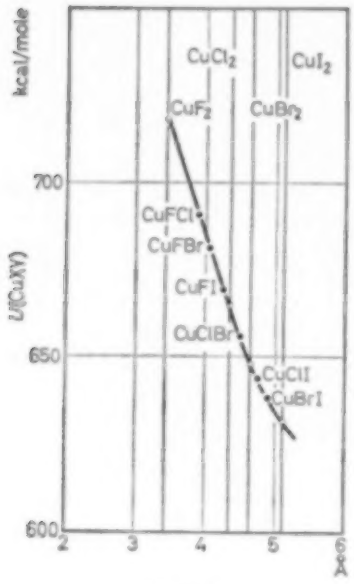

Figure 6

Tableau 8. Constantes thermodynamiques normales des halogénures cuivriques

	U (kcal/mole)	$\Delta H°(CuXY_{(c.)})$ (kcal/mole)	$S°(CuXY_{(c.)})$ (u.e.)	$\Delta G°(CuXY_{(c.)})$ (kcal/mole)
CuF_2	728	− 127	20	− 120
$CuCl_2$	663	− 49	27	− 40
$CuBr_2$	648	− 28	33	− 31
CuI_2	631	+ 2	38	+ 1
CuFCl	691	− 86	23,6	− 75
CuFBr	682	− 72	25,8	− 65
CuFI	670	− 55	29,1	− 50
CuClBr	658	− 42	29,2	− 33
CuClI	644	− 22	32,5	− 17
CuBrI	638	− 12	34,7	− 10

libre normale $\Delta G°$ des réactions de formation à partir d'halogénure simple et d'halogène, sont rassemblées dans le *Tableau 9*.

L'examen de ce tableau montre que, de tous les composés supposés, seuls peuvent être considérés comme stables CuFCl, CuFBr et CuClBr. En fait, nous avons laissé de côté les dérivés fluorés (CuF est instable et se dismute en CuF_2 et Cu à 25°C). Ces résultats sont en accord avec les constatations faites lors d'essais de préparation du CuClBr, CuClI et CuBrI: seul a pu être préparé CuClBr, poudre noire, très hygroscopique et d'aspect semblable aux chlorure et bromure cuivriques.

Tableau 9. Enthalpies libres normales des réactions de formation des halogénures cuivriques

	$\Delta G°$ (kcal/mole)
$CuF_{(c.)} + \frac{1}{2} F_{2(g.)} \rightleftarrows CuF_{2(c.)}$	− 60
$CuCl_{(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows CuCl_{2(c.)}$	− 11
$CuBr_{(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CuBr_{2(c.)}$	− 6
$CuI_{(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CuI_{2(c.)}$	+ 18
$CuF_{(c.)} + \frac{1}{2} Cl_{2(g.)} \rightleftarrows CuFCl_{(c.)}$	− 19
$CuF_{(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CuFBr_{(c.)}$	− 9
$CuF_{(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CuFI_{(c.)}$	+ 6
$CuCl_{(c.)} + \frac{1}{2} Br_{2(l.)} \rightleftarrows CuClBr_{(c.)}$	− 6
$CuCl_{(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CuClI_{(c.)}$	+ 11
$CuBr_{(c.)} + \frac{1}{2} I_{2(c.)} \rightleftarrows CuBrI_{(c.)}$	+ 14

Étude du chlorobromure cuivrique

Les modes de préparation du chlorobromure cuivrique par voie humide n'ont pas été utilisés: malgré une desiccation sous vide poussé, en presénce d'anhydride phosphorique, on ne parvient pas à éliminer toutes les inclusions de solvant et les pressions de dissociation mesurées sont très nettement supérieures aux valeurs réelles[27].

La préparation par voie sèche met à profit la réaction de formation $CuCl + \frac{1}{2}Br_2 \rightleftarrows CuClBr$. Le chlorure cuivreux, obtenu par voie humide (action de l'acide chlorhydrique R.P. sur du cuivre électrolytique) est desséché sous vide à 300° pendant plusieurs heures; en le maintenant ensuite à une température de 150° sous une pression notable de brome, la réaction est complète au bout de quelques heures; on laisse ensuite refroidir sous brome, puis le produit obtenu est laissé sous vide poussé pendant un temps suffisant pour éliminer les vapeurs résiduelles de brome.

Une analyse gravimétrique, faite avec une balance MacBain, montre que le corps obtenu correspond bien à la formule CuClBr.

Les tensions de dissociation ont été mesurées à l'aide d'un manomètre photoélectrique et d'un isotensioscope à acide phosphorique.

Le manomètre de verre à détection photoélectrique, mis au point au laboratoire[27, 28], a été décrit précédemment et nous n'y avons apporté que de légères modifications. L'élément de détection (*Figure 7*) est une membrane de verre M, très mince, au centre de laquelle appuie une tige de verre T, dont l'autre extrémité est soudée à un ressort en tungstène R, lui-même soudé à la paroi interne du tube de compensation C. Cette tige supporte une lame P, demi-cylindrique, de diamètre très légèrement inférieur au tube C.

Deux autres lames, L et L′, sont fixées au tube C et ménagent deux fentes fines entre elles et la lame mobile P. Une source lumineuse éclaire ces deux fentes qui délimitent deux faisceaux distincts; après avoir traversé une lentille cylindrique D, ces deux faisceaux tombent sur deux cellules photoélectriques E et E′ en opposition aux bornes d'un galvanomètre G.

Quand la même pression règne de part et d'autre de la membrane, le galvanomètre G ne dévie pas; mais il dévie dans un sens ou dans l'autre lorsque l'équilibre des pressions n'est plus réalisé: le dispositif de détection est basé sur une méthode de zéro de grande sensibilité.

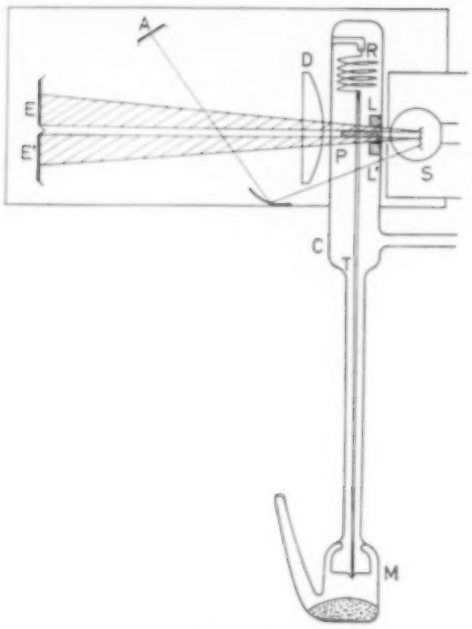

Figure 7

Le zéro est en principe indépendant de l'intensité de la source; en fait, comme les cellules E et E′ n'ont jamais exactement la même sensibilité, on rend la luminance de la lampe constante en montant son filament sur l'un des bras d'un pont de Wheatstone que l'on maintient équilibré. Une cellule photoélectrique auxiliaire A permet un contrôle constant de la luminance de la lampe.

La *Figure 8* montre l'ensemble du dispositif expérimental. L'ampoule manométrique, contenant le produit étudié, plonge dans un four muni d'une régulation fine. La température est mesurée par la méthode potentiométrique, au moyen de couples platine–platine rhodié.

Pour éviter tout risque d'hydratation, la synthèse du produit est réalisée dans l'ampoule même. On a donc prévu un ensemble F de pièges (à air liquide, à anhydride phosphorique, à charbon actif) et une réserve de brome B. La synthèse terminée, l'ampoule est scellée sous vide. Le vide est établi dans le tube de compensation par le robinet R_1. Les robinets R_2 et R_3 permettent d'ajuster finement la contrepression.

L'isotensioscope I qui sépare le mercure du brome émis, est rempli d'acide phosphorique pur (*Figure 9*). Le produit étudié est disposé dans l'ampoule A, placée dans un four muni d'une régulation fine de température. Les variations de températures doivent toujours être lentes, pour permettre une compensation continue de pression.

Pour éviter une condensation de brome lorsque la tension de dissociation devient égale à la tension de vapeur du brome à la température ambiante (la tension de vapeur du brome est d'environ 200 mm de mercure à 20°C)

VOL. 2 1961

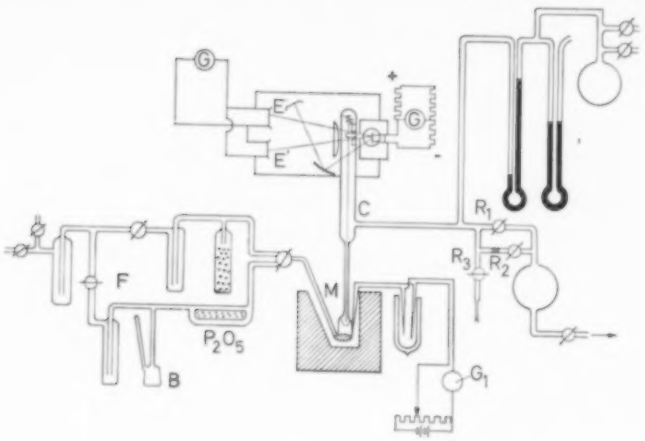

Figure 8

tout l'ensemble est placé dans un vaste thermostat à air T, maintenu à 60°C (dispositifs de commande et de régulation M et M') ce qui nécessite l'introduction d'une correction due à la tension de vapeur de l'acide phosphorique. Un jeu de robinets permet la compensation des pressions.

Comme pour le manomètre à membrane de verre, la synthèse du produit est réalisée dans l'appareil même.

Nous avons réalisé plusieures séries d'expériences, avec des échantillons différents de chlorobromure cuivrique. Les résultats obtenus sont comparables. L'équilibre a été abordé par températures croissantes et températures décroissantes; à chaque palier de température, il convient d'attendre que l'équilibre soit complètement atteint, ce qui peut demander plusieures heures à basse température.

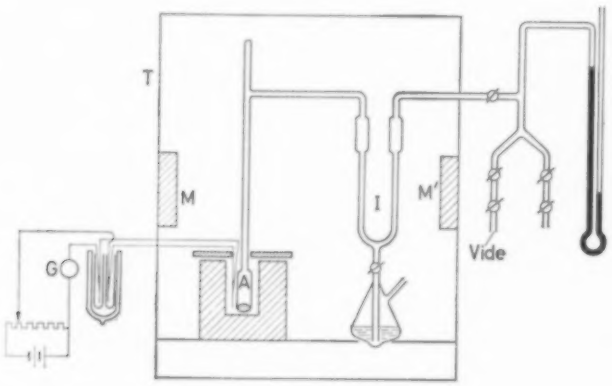

Figure 9

Les résultats expérimentaux sont reportés sur les *Figures 10* et *11*.

La droite expérimentale de la *Figure 11*, où ont été portés en ordonnée le logarithme décimal des tensions de dissociation et en abcisse l'inverse des températures absolues, a pour équation:

$$\log p(\text{atm}) = -\frac{3448{,}2}{T} + 5{,}63$$

Il est intéressant de comparer les valeurs calculées par notre méthode, aux valeurs expérimentales des enthalpies libres normales et enthalpies normales de la réaction (*Tableau 10*):

$$CuCl_{(c.)} + \tfrac{1}{2}Br_{2(l.)} \rightleftharpoons CuClBr_{(c.)}$$

Compte tenu des approximations faites, la concordance nous parait satisfaisante.

Tableau 10

(*a*) *Enthalpie libre normale et enthalpie normale de la réaction:* $CuCl_{(c.)} + \frac{1}{2}Br_{2(l.)} \rightleftharpoons CuClBr_{(c.)}$

$\Delta G°$ (kcal/mole)		$\Delta H°$ (kcal/mole)	
Calculée	*Expérimentale*	*Calculée*	*Expérimentale*
−6	−7,12	−16	−15,800

(*b*) *Grandeurs thermodynamiques normales de* CuClBr

$G°$ (kcal/mole)		$H°$ (kcal/mole)	
Calculée	*Expérimentale*	*Calculée*	*Expérimentale*
−42	−44,0	−33	−35,1

Nous avons également reporté sur la *Figure 11* les résultats trouvés[29-31] pour les tensions de dissociation de $CuCl_2$ et nos propres résultats pour les tensions de dissociation de $CuBr_2$:

$$\log p(\text{atm}) = -\frac{3846{,}3}{T} + 6{,}81$$

qui, un peu différents, mais du même ordre de grandeur que ceux donnés dans des travaux récents[27, 29], s'écartent eux aussi considérablement de ceux donnés dans des travaux plus anciens[32].

A partir des valeurs des grandeurs thermodynamiques normales, à 25°, du chlorure cuivreux[2, 4, 29], les grandeurs thermodynamiques normales du chlorobromure cuivrique peuvent être calculées (*Tableau 10*).

CONCLUSION

Les fonctions thermodynamiques normales d'halogénures mixtes hypothétiques MX_mY_n, qui peuvent être évaluées avec une précision satisfaisante, fournissent le moyen de prévoir l'existence de tels composés. Les

VOL. 2 1961

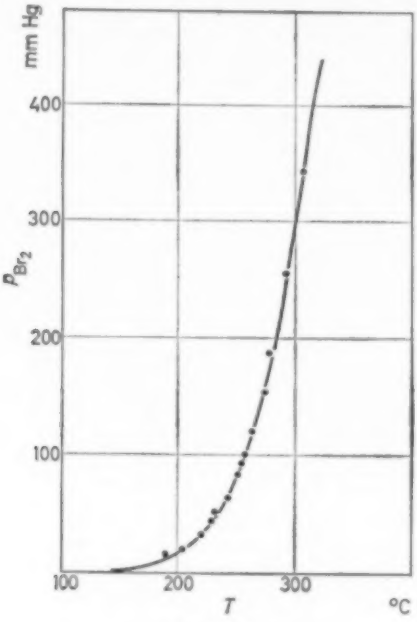

Figure 10

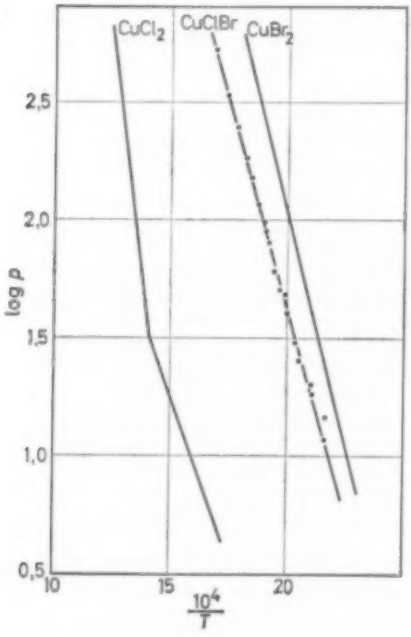

Figure 11

valeurs calculées par cette méthode pour le chlorobromure cuivrique, sont en bon accord avec les valeurs tirées de l'étude de la réaction de dissociation:

$$CuClBr \rightleftharpoons CuCl + \tfrac{1}{2} Br_2$$

Cette réaction est réversible et la combinaison, par voie sèche, du brome gazeux sec et du chlorure cuivreux calciné sous vide, conduit facilement, de façon stoechiométrique, à un produit parfaitement anhydre.

Les halogénures mixtes appartiennent à une classe bien particulière de corps et il ne semble pas que l'on doive les envisager comme des solutions solides idéales d'halogénures simples; on peut les considérer comme des corps parfaitement définis, intermédiaires qui s'intercalent entre les halogénures simples.

Dans le cas particulier du chlorobromure cuivrique, la décomposition thermique, suivie par gravimétrie, aboutit toujours au chlorure cuivreux: la réaction suit vraisemblablement le schéma le plus simple envisagé précédemment, $CuClBr \rightleftharpoons CuCl + \frac{1}{2} Br_2$, sans qu'il soit nécessaire de recourir à un schéma de réaction plus compliqué et probablement moins vraisemblable, tel que $CuCl_2 + CuBr_2 \rightleftharpoons 2\ CuCl + Br_2$.

De plus, le chlorobromure cuivrique possède un diagramme de rayon X propre. Ce diagramme de poudre paraît s'intercaler entre ceux obtenus pour le chlorure et le bromure cuivriques, bien qu'il soit nettement différent de chacun d'eux. Dans un prochain travail, nous nous proposons de préciser les propriétés cristallines du chlorobromure et d'en comparer la structure aux structures connues, des chlorure et bromure cuivriques.

Je tiens, en terminant, à remercier Monsieur le Professeur Barret de l'intérêt bienveillant qu'il a porté à la réalisation de ce travail.

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VOL.
2
1961

EQUILIBRIUM STUDIES ON DISULPHIDES USING VAPOUR PHASE CHROMATOGRAPHY*

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It is a well-known fact that disulphides undergo disproportionation reactions according to

$$R'SSR' + R''SSR'' \rightleftharpoons 2R'SSR''$$

This reaction has been used particularly for the synthesis of unsymmetrical disulphides[1–5] and McAllan *et al.*[5] have shown that the position of the equilibrium depends on the nature of R′ and R″. When R′,R″ are n-alkyl groups the expected statistical distribution $(R'S)_2$: $R'R''S_2$: $(R'S)_2 = 1:2:1$ is reached, whereas for R′ = Et and R″ = *sec*-Bu and *tert*-Bu the ratios were found to be close to 1 : 4, 5 : 1 and 1 : 6 : 1, respectively.

The disproportionation reaction occurs either in the presence of an ionic catalyst such as NaOH, Na_2S, or *tert*-BuSNa, or upon irradiation with ultra-violet light.

During the course of an investigation on the energetics of the disulphide bond it became important to determine the equilibrium constants for a number of dialkyl disulphides. Calvin *et al.*[6] used the u.v.-spectrophotometric method to determine the equilibrium constant for a slightly different type of reaction, namely

$$BzSSBz + HS(CH_2)_3SH \rightleftharpoons 2BzSH + \underline{S(CH_2)_3S}$$

This method could be used in this case as the 1,2-dithiolane ring has an absorption maximum at 330mμ, whereas open-chain dialkyl disulphides show a peak at *ca.* 250 mμ.

DISCUSSION OF METHOD

Vapour phase chromatography provides an obvious solution to the problem of finding an appropriate method for the separation and quantitative determination of the homologous dialkyl disulphides. This technique seems to offer a number of advantages for equilibrium studies, particularly on fairly simple systems.

(1) The separation efficiency can be made very high. The quantitative separation of *e.g.* Et_2S_2, *i*–$PrEtS_2$ and *i*–Pr_2S_2 can be achieved on a column only 120 cm in length.

(2) The presence of impurities formed in side reactions is instantaneously revealed in the chromatogram.

(3) The analysis is rapid, a run being completed within *ca.* 20 min. It is therefore frequently possible to determine the reaction rate by analysing samples from time to time.

*Published in *Acta Chem. Scand.*, **14**, 1509 (1960)

(4) The size of the sample can be very small—with a sensitive detector as little as 0·025 μl is sufficient. Thus, equilibrium conditions can be studied in a gas mixture at low pressures without increasing the volume of the system inconveniently.

Two conditions must be fulfilled to make the vapour phase chromatographic method useful.

(1) A linear relationship must exist between the amplified signal from the detector and the amount of substance passing the detector per unit time. Then the area under the peak of the chromatogram must be proportional to the total amount of substance. Within certain limits this can be achieved with different types of detectors, although some of them require carefully controlled operating conditions.

(2) Usually, the chromatographic column is operated at a temperature different from that at which the equilibrium is studied. It is therefore a necessary requirement that no reaction takes place on the column.

Both conditions can easily be tested with mixtures of known composition.

Calculation

To a good approximation, the equilibrium constant for the disproportionation reaction taking place in an inert hydrocarbon solution can be written

$$K = \frac{m_{12}^2}{m_{11} \times m_{22}}$$

where m_{11} and m_{22} are the molalities of the two symmetrical disulphides and m_{12} that of the unsymmetrical one. In a sample, the ratio between two molalities is identical with the ratio between the number of moles, n, of the corresponding components. The vapour phase chromatograph is operated under such conditions as to fulfil the relation $n_i = k_i \times y_i$, where k is a constant and y an area under a peak on the chromatogram, k and y being both related to the component i. In the present case one of the reaction participants can be used as a reference substance, thus

$$\frac{n_i}{n_j} = \frac{k_i}{k_j} \times \frac{y_i}{y_j} = k \times \frac{y_i}{y_j}$$

Hence

$$K = \frac{n_{12}}{n_{11}} \times \frac{n_{12}}{n_{22}} = k'k'' \frac{y_{12}}{y_{11}} \times \frac{y_{12}}{y_{22}}$$

The two constants k are evaluated from calibration experiments with known mixtures of disulphides and the areas y are measured with a planimeter or an electronic integrator.

EXPERIMENTAL

In the present investigation a Pye Argon chromatograph was used with a 5 mm column, 120 cm in length, filled with 100–120 mesh size crushed brick stone containing 5 per cent by weight of Apiezon grease L. For the pair of disulphides, Me_2S_2 and Et_2S_2, the temperature was kept at 104°C.

VOL. 2 1961

Calibration was carried out with all three pairs of disulphides. Mixtures of dimethyl and diethyl disulphide in the molar ratios 2 : 1, 1 : 1 and 1 : 2 gave values of the corresponding constant, k''',

$$\frac{n_{11}}{n_{22}} = k''' \times \frac{y_{11}}{y_{22}}$$

equal to $0{\cdot}89 \pm 0{\cdot}22$, $0{\cdot}91 \pm 0{\cdot}03$ and $0{\cdot}88 \pm 0{\cdot}03$, respectively. The methyl ethyl disulphide was prepared by the disproportionation reaction and the mixture was carefully distilled. A fraction containing 96 per cent of $MeEtS_2$ and 4 per cent of Me_2S_2 (as determined by vapour phase chromatography) was used and appropriate corrections for the presence of Me_2S_2 were applied. The two constants were found to be: $k' = 1{\cdot}03 \pm 0{\cdot}02$ and $k'' = 0{\cdot}96 \pm 0{\cdot}22$. The ratio k''/k', which by definition is equal to k''', thus becomes $0{\cdot}93 \pm 0{\cdot}03$, to be compared with the experimental (average) value $0{\cdot}90 \pm 0{\cdot}02$. When Apiezon grease was used as the stationary phase no detectable disproportionation reaction occurred on the column.

All experiments were carried out in a cyclohexane solution and the total concentration of disulphides present was in most cases kept close to one mole per litre. The equilibrium was reached from both sides and the equilibration was brought about both by an ionic catalyst (NaOH) and by irradiation with light from a low pressure mercury lamp. Experiments were carried out at 25°C and at 60°C. The solutions treated with sodium hydroxide were kept in 7 × 100 mm test-tubes with ground glass stoppers. The catalyst was deposited as a very thin film on the inner surface of the tube before the solution was introduced. The irradiated solutions were kept in quartz tubes. Under the prevailing conditions equilibrium was established within 4 days in experiments with NaOH or within 4 hours of irradiation.

RESULTS

The results from the measurements on the pair dimethyl disulphide and diethyl disulphide are summarized in *Table 1*. The third column gives the side from which equilibrium has been reached. From the table it is evident that a true equilibrium has been reached and that the temperature dependence of the equilibrium constant is less than the uncertainty of the results.

Table 1

Temp. (°C)	*Treatment*	*Starting from*	*K*
25	NaOH	symm.	$5{\cdot}2 \pm 0{\cdot}2$
25	light	symm.	$5{\cdot}0 \pm 0{\cdot}2$
25	NaOH	unsymm.	$5{\cdot}4 \pm 0{\cdot}1$
25	light	unsymm.	$5{\cdot}7 \pm 0{\cdot}2$
60	NaOH	symm.	$5{\cdot}1 \pm 0{\cdot}2$
60	NaOH	unsymm.	$5{\cdot}6 \pm 0{\cdot}1$

This investigation has been carried out under Contract AF 61 (052)–46 with Air Research and Development Command, United States Air Force, through its European Office.

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VOL
2
1961

ZUR THERMOCHEMIE DER TRITHIOKARBONATE*

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Kürzlich konnte durch Bestimmung der Dampfdrucke von Zn, Se und Te gezeigt werden[1], daß das modifizierte Verfahren zur Messung von Dampfdrucken nach Baur und Brunner[2] allgemein anwendbar ist und größenordnungsmäßig gleich genau zu sein scheint wie die bisher bekannten Verfahren.

Dieses statische Verfahren beruht auf der Ermittlung des Siedepunktes einer Substanz bei vorgegebenem Druck. Das Füllgas des Verdampfungsgefäßes, das die Substanz enthält, ist durch einen Quecksilber-Tropfen, der sich in einer horizontalen Glaskapillare (mit eingeätzter mm-Strichteilung) befindet, von einem großen Vorratsvolumen abgetrennt (nähere Einzelheiten siehe[1]). Bei kontinuierlicher Temperaturerhöhung bewegt sich der Hg-Tropfen nur sehr wenig (entsprechend der thermischen Ausdehnung des Füllgases), bis die Siedetemperatur unter dem vorgegebenen Druck erreicht ist, worauf der Tropfen mit einer ziemlich schnellen, aber konstanten Bewegung antwortet. Zur Auswertung der Versuche wird die Lage des Hg-Tropfens (in Skalenteile) gegen die jeweilige Temperatur aufgetragen; die Siedetemperatur wird graphisch ermittelt (*Abb. 1*).

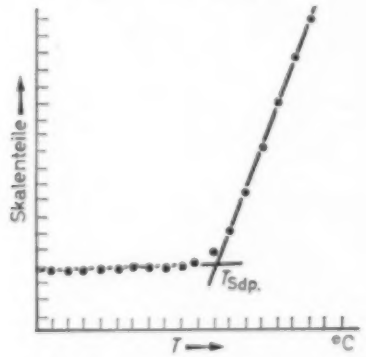

Abb. 1. Lage des Hg-Tropfens mit steigender Temperatur

Die Methode ist sowohl für tiefere[3] (30°C) als auch für hohe Temperaturen[4] (1300°C) und im Druckbereich zwischen etwa 5 und 150 mm Hg anwendbar; sie liefert reproduzierbare Ergebnisse, sofern die Aufheizgeschwindigkeit nicht 5,5°C/min überschreitet. Die benötigte Substanzmenge ist von Substanz zu Substanz verschieden und beträgt *ca.* 100 bis 500 mg; Dauer einer Messung: *ca.* 30 min.

* Bestimmung von Dissoziationsdrucken nach dem Verfahren von Baur und Brunner[2].

Untersuchungen an Tl_2CO_3 zeigten, daß diese Methode universell für die Ermittlung von Dissoziationsdrucken anwendbar ist. Neben Tl_2CO_3 wurden die Dissoziationsdrucke von Tl_2CS_3 und $BaCS_3$ bestimmt, nachdem thermogravimetrisch der Zersetzungsmechanismus und durch isobaren Abbau die Gleichgewichtseinstellung der Systeme gesichert werden konnte:

$$Tl_2CO_{3(flüss.)} \longrightarrow Tl_2O_{(gelöst)} + CO_{2(Gas)}$$

$$Tl_2CS_{3(fest)} \longrightarrow Tl_2S_{(fest)} + CS_{2(Gas)}$$

$$BaCS_{3(fest)} \longrightarrow BaS_{(fest)} + CS_{2(Gas)}$$

Aus der Temperaturabhängigkeit der Dissoziationsdrucke wurden die freien Reaktionsenergien, die Bildungswärmen und Normalentropien dieser Verbindungen errechnit; die dafür notwendigen Daten wurden, soweit keine neueren Werte bekannt sind, dem Tabellenwerk von Kubaschewski und Evans[5] entnommen. Die Normalentropien von Tl_2O, Tl_2S und BaS wurden nach Latimer[6] und Turkdogan[7] berechnet und gemittelt (Tl_2O: 33,6 ± 1,5; Tl_2S: 39,0 ± 0,5; BaS: 21,5 ± 1,0 cal °C^{-1} Mol^{-1}).

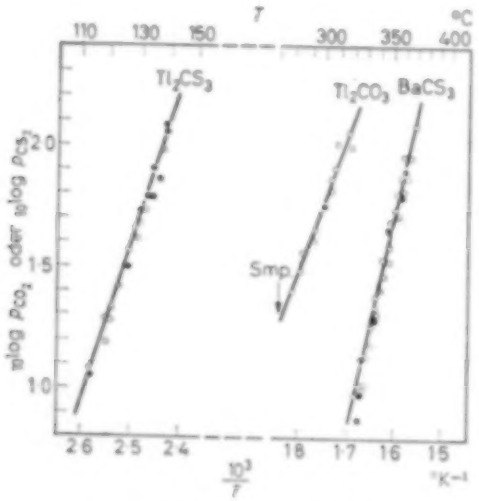

Abb. 2. Dissoziationsdrucke von Tl_2CO_3, Tl_2CS_3 und $BaCS_3$: ○ Füllgas: N_2; ● Füllgas: CO_2 bzw. CS_2

Zusammengefaßt ergeben sich für die Dissoziationsdrucke (in mm Hg)

$$_{10}\log p = -\frac{10^3 A}{T} + B$$

(*Abb. 2*), für die Reaktionswärmen ΔH_R, Reaktionsentropien ΔS_R, freie Energien $\Delta G = \Delta H_R - T\Delta S_R$ der Zersetzungsreaktionen im gemessenen Temperaturbereich und für die Bildungswärmen $\Delta H_{B298°K}$ und Normalentropien $S_{298°K}$ der festen Verbindungen die in *Tabelle 1* aufgeführten Werte.

Die Messungen werden auf weitere Karbonate und Trithiokarbonate ausgedehnt.

Tabelle 1. Thermochemische Daten von Tl_2CO_3, Tl_2CS_3 und $BaCS_3$

	Tl_2CO_3	Tl_2CS_3	$BaCS_3$
Aufheizgeschwindigkeit (°C/min)	3,0 ± 0,5	3,0 ± 0,5	4,0 ± 0,5
Füllgas	CO_2, N_2	CS_2, N_2	CS_2, N_2
Anzahl der Messpunkte	12	21	32
Temperaturbereich (°C)	275–320	110–145	320–360
A	5,934	6,061	9,876
B	12,136	16,689	17,506
ΔH_R (kcal/Mol)	27,1$_4$ ± 0,7	27,7$_8$ ± 0,7	45,2 ± 1,5
ΔS_R (cal °C^{-1} Mol^{-1})	42,3 ± 1,2	63,2 ± 1,3	66,9 ± 2,0
$\Delta H_{R298°K}$ (kcal/Mol)	− 168,1 ± 1,7*	− 21,0 ± 2,0	− 130,1 ± 3,0
$\Delta S_{298°K}$ (cal °C^{-1} Mol^{-1})	34,3 ± 3,0	32,6 ± 3,0	11,2 ± 5,0

* Aus E.M.K.-Messungen erhielt Saegusa[8] einen Wert von − 167,2 kcal/Mol.

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VOL
2
1961

THE HEATS OF COMBUSTION OF PHENOL AND THE THREE CRESOLS

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Precise measurements of the thermodynamic properties of phenol and some of its homologues are being made in this Laboratory. As part of this programme, the heats of combustion of phenol and the three cresols (methylphenols) have been accurately determined and are here reported; the heats of combustion of the six xylenols (dimethylphenols) will be reported elsewhere.

The combustion calorimetry of the phenols involves the difficulty that these compounds are somewhat hygroscopic and are prone to oxidation by air or oxygen. Additionally, phenol and its lower homologues, although most are solids at 25°, have vapour pressures at 25° which are too great to permit their being placed unenclosed within a combustion bomb, when work of high precision is attempted. These problems were all overcome in the present work by sealing pellets of the solid phenols inside polyethylene bags, which were then placed inside the crucible of the combustion bomb. Experiments on *m*-cresol, a viscous liquid at 25°, were also conducted with samples sealed in polyethylene bags, in order to make the conditions of measurement closely comparable with those adopted for the solid phenols.

The polyethylene bags were rectangular (25 mm × 30 mm; average mass 0·09 g), and were made from polyethylene film 0·05 mm thick. To make the edges of the bag, two surfaces of the film were sealed together by means of a low-temperature soldering iron having a wheel-and-axle bit. Pellets of a solid phenol were prepared in a " dry-box " and were placed inside a weighed open-ended polythene bag; in the case of *m*-cresol, the liquid was pipetted into a weighed bag. The bag was then sealed, and the whole weighed. The bag and contents were placed inside the platinum crucible of the bomb[1, 2], and platinum fuse wire, connected to the bomb's firing circuit, was placed in contact with the top surface of the bag. With this arrangement, passage of a current through the fuse wire always ignited the bag and its contents, no kindling material other than the bag being required.

The general technique used in the combustion experiments has been described[1–3]. The energy equivalent of the calorimeter was determined electrically, and all temperature measurements were made with a platinum resistance thermometer. The energy of combustion, ΔU_c°, of the polyethylene film was measured as -46427 ± 9 J/g. The samples of the phenols used were prepared in this Laboratory; sample purities were determined by a freezing point method and exceeded 99·9 moles per cent in every instance. Mean values for the standard heats of combustion, ΔH_c°, of phenol and the cresols are summarized in *Table 1*. The uncertainties

quoted are standard deviations of the mean and include a small contribution from the uncertainty in the energy equivalent of the calorimeter; the "uncertainty interval" of each value in the table is by definition twice the given standard deviation of the mean.

The literature contains only one modern reference to the heat of combustion of phenol (and none to that of the cresols) which might be compared with the value reported in the table. Thus Parks, Manchester and Vaughan[4] gave −730·36 kcal/mole as ΔH_c° for phenol. The discrepancy between this value and ours falls just outside the sum of the two uncertainty intervals, but as Parks, Manchester and Vaughan's paper contains no experimental details, further comment is not possible.

Table 1. Heats of combustion of phenol and the cresols. "Thermochemical" calories. 1 cal = 4·1840 abs. J.

Compound	*State at 25°*	$-\Delta H_c^\circ$ (kcal/mole)	$-\Delta H_f^\circ$ (kcal/mole)	$-\Delta H_f^\bullet$ (kcale/mole)
Phenol	cryst.	729·82 ± 0·07	39·44	23·03 ± 0·14
o-Cresol	cryst.	882·79 ± 0·10	48·84	30·67 ± 0·21
m-Cresol	liquid	885·44 ± 0·06	46·19	31·44 ± 0·26
p-Cresol	cryst.	884·02 ± 0·07	47·61	29·94 ± 0·36

VOL. 2 1961

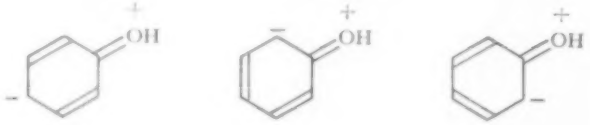
The fourth column of the table contains values of the standard heats of formation from the elements, ΔH_f°, as calculated from values of ΔH_c° with the aid of values for the heats of formation of carbon dioxide and water[5]. The last column of the table contains values of the heats of formation of the compounds at 25°C in the ideal gas state, $\Delta H_f^\bullet$. Strictly, these values refer to the real gases, but the vapour pressures of the compounds at 25° are sufficiently low for the values to be indistinguishable from those for the ideal gas. Values of the latent heats of sublimation (or latent heat of vaporization for the liquid *m*-cresol), required for the calculation of $\Delta H_f^\bullet$, were taken from the work of Biddiscombe and Martin[6] of this Laboratory. These workers made careful measurements of the vapour pressures of phenol and the cresols in the region of 25°, and from their measurements calculated the latent heats of sublimation (or vaporization). The uncertainties quoted in the last column of the table were obtained by combining the standard deviations of the ΔH_c values with those of the latent heats, assuming that there are no errors in ΔH° for carbon dioxide and water.

With values of $\Delta H_f^\bullet$ available, the calculation of the resonance energies of phenol and the cresols was attempted by the well-known procedure of calculating the heats of formation from the atoms in their ground states, and comparing the results with values obtained by summing bond energy terms. Calculations were made from values for the heats of atomization of the elements and bond energies taken from three different compilations[7–9]. Similar results were obtained from each compilation, so that it is only necessary to choose one of them for a detailed discussion. The compilation chosen for the present purpose is that of Laidler[9], which is not only the most recent of the three but also appears to be the most precise. Laidler's bond energy scheme takes account of the various types of C—H bonds

(primary, secondary or tertiary) in the molecule, and also of the types and positions of C—H bonds with respect to C=C bonds. The resonance energies of phenol and the cresols, when calculated from the present values of ΔH_f° with the aid of Laidler's data, were as follows:

phenol 44·7 kcal/mole; benzene 42·8 kcal/mole
o-cresol 44·2 kcal/mole;
m-cresol 45·0 (kcal/mole); toluene 42·5 kcal/mole
p-cresol 43·5 (kcal/mole).

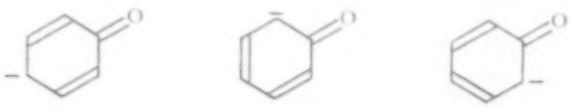
For purposes of comparison, the resonance energies of benzene and toluene, taken from Laidler's paper[9], have been included in the above table. Considering first phenol relative to benzene, it may be seen that the resonance energy of the former appears to be about 2 kcal/mole greater than the resonance energy of the latter. Qualitatively, this situation was to be anticipated because the resonance structures of phenol would be expected to include the quinonoid forms (I), (II) and (III):



(I) (II) (III)

in addition to the normal Kekulé and Dewar forms of the benzene ring. Hitherto, however, heat of formation data for phenol have been insufficiently reliable to show whether or not these resonance forms made a measurable contribution to the resonance energy[10]. It is therefore important to consider carefully whether the apparent 2 kcal/mole difference between the resonance energies of phenol and benzene is real. Errors in the values of ΔH_f° for the two compounds are unlikely to exceed 0·5 kcal/mole, but errors greater than this may be involved in the calculation of atomic heats of formation and total bond energies. Fortunately these errors will mainly affect the absolute values of the two resonance energies, rather than their difference, since most of the data used are common to the two calculations. Data which are *not* common to the two calculations relate to the C—OH bond. Laidler[9] recommends that a "mean" bond energy term of 198·1 kcal be used for the C—OH bond; at present, too few reliable values of the heats of formation of aliphatic alcohols exist to permit making a distinction between the C—OH bond energies in primary, secondary and tertiary alcohols. From Roberts and Skinner's[11] summary of bond energy data for alcohols it seems that the mean bond energy for C—OH must be considered uncertain to ± 2 kcal. As this uncertainty is the dominant one in a comparison of phenol with benzene, it may be concluded that the extra resonance stabilization of phenol relative to benzene lies within the limits 0 to 4 kcal/mole. When a more reliable value becomes available for the C—OH bond energy term, it should be possible to define the extra resonance stabilization of phenol within closer limits.

If attention is confined to intercomparison of phenol and the cresols, the uncertainty of the C—OH bond energy becomes irrelevant. It may then be seen that the resonance energies of phenol and *m*-cresol are indistinguishable within the combined standard errors, whereas the resonance energies of *o*- and *p*-cresol are slightly less than the resonance energy of *m*-cresol. A parallel to this situation is found in the acidities of these compounds, where phenol and *m*-cresol have closely similar acidities in water[12], whilst *o*- and *p*-cresol are appreciably weaker acids. An explanation for the parallel presents itself when it is remembered that the appreciable acidity of phenol may be ascribed[10] to the contribution of structures (IV), (V) and (VI) to the resonance in the phenolate ion.



(IV) (V) (VI)

Substitution of a *m*-methyl group into either phenol or phenolate ion would not be expected to influence the contributions of quinonoid structures (I)–(III) or (IV)–(VI). Hence phenol and *m*-cresol should have closely similar resonance energies and acidities. On the other hand, substitution of *o*- or *p*-methyl groups would be expected to discourage the placing of a negative charge (structures (I)–(III) or (IV)–(VI)) on the carbon atoms to which the methyl groups are attached, i.e. *o*- and *p*-cresol should have smaller resonance energies and acidities than *m*-cresol.

I wish to thank several of my colleagues for preparing and certifying the samples of the phenols, and Messrs R. J. L. Andon and H. A. Gundry for their work on the calorimetric measurements.

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VOL. 2 1961

HEATS OF COMBUSTION OF BUTANAL AND SOME RELATED COMPOUNDS*

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Precision data on heats of combustion of aliphatic aldehydes are lacking in the literature and since the appearance of Kharasch's compilation[1] no further determinations have been published. Therefore it was judged of interest to study a number of aliphatic aldehydes. The choice of compounds was mainly governed by an interest in the aldol condensation reaction and associated processes for butanal.

SAMPLE PURITY

It is a well-known fact that simple aliphatic aldehydes are difficult to obtain in a very pure state and this work has given no evidence for expressing an opposite opinion. Before describing the special problems met with in handling the aldehydes, the general procedure for preparing the samples for combustion will be given.

Procedure

All six substances used in this investigation were prepared and carefully purified by the Research Laboratory, Mo and Domsjö Aktiebolag, Örnsköldsvik, Sweden. After the final distillation in a Podbielniak column with 50–70 theoretical plates, samples of the main fraction were enclosed in sealed Pyrex-glass ampoules in an atmosphere of nitrogen or helium. On the contents of one of these ampoules the purity was established using gas–liquid chromatography, and a number of ampoules were sent without delay to our laboratory. Immediately upon arrival (2–3 days later) a distillation was performed at room temperature under reduced pressure. All samples were handled in a nitrogen atmosphere and utmost care was taken to exclude air. The middle fraction from this distillation (about one-third of the total sample) was collected in a receiver where some ten combustion ampoules (made from soft glass) had been placed in advance, and these were immediately sealed[2]. At the same time ampoules were filled with samples for gas–liquid chromatographic analysis and for density determination. The combustions were made as soon as possible, and in no case more than six days elapsed between ampoule filling and the last combustion. In the case of butanal all experiments were carried out within two days. Analysis (by Mo and Domsjö) and density determination were performed so as to coincide in time with the middle experiment in the combustion series.

The gas–liquid chromatographic analysis was done in order to determine the amount of impurities, especially water. For all substances except butanal the area under the water peak on the chromatogram was pro-

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portional to the water content of the sample, which was found from calibration experiments with known amounts of water added to the sample. The linearity implies that no reaction leading to the formation of water occurred on the column. In the case of butanal, however, a reaction took place on the column with formation of water.

The water content of the butanal sample was evaluated using the observation that the density of a sample of this compound varied linearly with the water content, at least over a small range. A sample of butanal was prepared exactly as the material for combustion. This sample was divided into three parts and water was added to two of them, increasing the amount of water by 0·275 and 0·551 per cent, respectively. The densities of the three parts were determined (*Table 1*).

Table 1. Density and water content of butanal

Water (%)	d_4^{25} (g/ml)
x	$0{\cdot}7966_9 \pm 0{\cdot}0000_2$
$x + 0{\cdot}275$	$0{\cdot}7976_1 \pm 0{\cdot}0000_8$
$x + 0{\cdot}551$	$0{\cdot}7988_3 \pm 0{\cdot}0000_8$

The slope of the line, density *versus* per cent water, was calculated, and a line was drawn using the value of Smith and Bonner[3]: $d_4^{25} = 0{\cdot}7964$ at 0·03 per cent of water. The density 0·7966 then corresponds to a water content of $0{\cdot}08 \pm 0{\cdot}02$ per cent.

VOL. 2 1961

Special problems

The unsaturated aldehydes studied were found to be stable during storage in Pyrex ampoules for two weeks. However, distillation at temperatures higher than *ca.* 50°C caused rapid decomposition. The sensitivity towards oxidation was found to be very pronounced, and it was therefore necessary to exclude even traces of air in handling these compounds. Butanal was found to be unstable even when every precaution was taken in storing the samples. The decomposition was followed by measuring the density, and an increase in d_4^{25} of 0·00003 per day was observed. Distillation of butanal above room temperature caused an increase in water content and in amounts of other impurities. When distillation was performed at room temperature with the receiver kept at −40° to −80°C, the distillate showed a marked tendency to polymerize to solid products. A few successful distillations were performed with the receiver kept at −20°C and the distilling flask at 35°C (pressure 40–50 mm Hg).

In a number of cases condensation of butanal took place within the combustion ampoule, which then invariably burst. This was shown by the following series of experiments. Twelve ampoules (of the combustion type) were filled with butanal and left to stand for some days. During this time several ampoules burst. Now and then one of the intact ampoules was opened, and in both cases the refractive index of the content was immediately determined. The refractive index of the content was unchanged for all intact ampoules, but had altered for every broken ampoule, usually by about 0·002 units.

2-Ethylhexanal offered the same kind of handling difficulties as did butanal but to a much smaller extent. Distillation could be performed at 85°C and 35 mm Hg, and gas–liquid chromatograms were successfully run at 150°C. With the alcohols of this investigation no special problems were met, and the analyses showed that perfect purity was obtained in both cases.

Results of purity determinations

In *Table 2* values of densities and amounts of impurities have been summarized. For comparison, density values found in the literature have also been given.

Table 2. Sample purity

Substance	d_4^{20} (g/ml)	d_4^{25} (g/ml)	H_2O (%)	*Org.* (%)	*Literature*
2-Butenal	0·8526	0·8475	0·02	0·05	$d_4^{17.5} = 0{\cdot}8557$[4]
Butanal	—	0·7966	0·08	—	$d_4^{20} = 0{\cdot}7964$ (0·03% H_2O[5])
1-Butanol	0·8099	0·8059	0	0	$d_4^{25} = 0{\cdot}8057$[5]
2-Ethylhex-2-enal	0·8522	0·8461	0·014	0·4	$d_4^{20} = 0{\cdot}8528$[6]
2-Ethylhexanal	0·8201	0·8156	0·03	0·7	$d_4^{20} = 0{\cdot}8231$[7]
2-Ethylhexan-1-ol	0·8332	0·8291	0	0	$d_4^{20} = 0{\cdot}8328$[8]

COMBUSTION CALORIMETRY

The calorimeter described by Bjellerup[9] was used without rotation of the bomb. Washburn corrections have been applied as described by Hubbard, Scott and Waddington[10]; the latter's procedure and the nomenclature given by them have been followed. Corrections for the water content of the samples have been applied.

Table 3. Thermochemical data, referring to the liquid standard state at 25°C*

Substance	$-\Delta E_c^\circ$ (kcal/mole)	$-\Delta H_c^\circ$ (kcal/mole)	$-\Delta H_f^\circ$ (kcal/mole)
2-Butenal	546·12 ± 0·09	546·71 ± 0·09	34·45 ± 0·09
Butanal	591·53 ± 0·17	592·42 ± 0·17	57·06 ± 0·17
1-Butanol	637·07 ± 0·10	638·25 ± 0·10	79·55 ± 0·10
2-Ethylhex-2-enal	1166·39 ± 0·17	1168·17 ± 0·17	62·46 ± 0·17
2-Ethylhexanal	1213·56 ± 0·18	1215·63 ± 0·18	83·32 ± 0·18
2-Ethylhexan-1-ol	1261·44 ± 0·19	1263·81 ± 0·19	103·46 ± 0·19

* The uncertainties given are the final overall standard deviations.

The final overall standard deviations include the errors of (1) the heat of combustion value for benzoic acid, (2) the calibration experiments, (3) the paraffin oil combustions, (4) the determination of weight including water analysis and finally (5) the standard deviation of the actual combustion series.

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VOL.
2
1961

HEATS OF COMBUSTION OF FIVE ALKYL PHENYL KETONES

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As a contribution to the determination of fundamental thermodynamic properties of pure organic compounds a group of alkyl phenyl ketones has been selected for study.

METHOD AND APPARATUS

The heats of combustion of the compounds were determined by burning the liquid alkyl phenyl ketones in oxygen in a bomb, at constant volume. The procedure is similar to that described by Prosen[1], followed by us in other studies[2].

Materials

The methyl, ethyl and propyl phenyl ketones were commercial products. The iso- or *tert*-butyl phenyl ketones were synthesized in this laboratory. The five ketones were purified first by vacuum distillation, in a column of fifty theoretical plates, and then by fractional melting, with an apparatus developed in this laboratory from a simpler device described by Nicholson[3]. The qualitative control of purity by heating curves, following the method of Skau, showed that these compounds were very pure.

EXPERIMENTAL RESULTS

The results of a series of calibration experiments using N.B.S. standard benzoic acid are given in *Table 1*. The tabulated data were obtained as in the following paper[2]. The values of q_1 were obtained from separate ignition experiments in which a standard mass of 8·30 mg of iron was burned (standard $q_1 = 62$ J).

Table 1. Data from calibrating experiments with benzoic acid

Expt No.	*Mass of benzoic acid* (g)	$\Delta\varepsilon_1$ (J/Ω)	ΔR_c (Ω)	q_1 (J)	q_n (J)	E_c (J/Ω)	*Deviation from mean* (J/Ω)
1	1·59823	19·2	0·299388	61·7	1·7	141294	− 25
2	1·59794	19·2	0·299233	62·0	1·9	141343	+ 25
3	1·59979	19·2	0·299624	61·8	2·0	141322	+ 3
4	1·60135	19·2	0·299945	63·8	1·9	141313	− 6
5	1·59822	19·2	0·299342	62·4	2·7	141320	+ 1
						Mean, 141319	
						S.D. of mean, ± 8	

In *Table 2* the results of five series of combustion experiments with the alkyl phenyl ketones are given. These data were obtained as in the following paper[2].

In *Table 3* the heats of combustion and formation of the five alkyl phenyl ketones are given. These data and their uncertainties were computed as in the following paper[2].

CONCLUSIONS

On comparing the heats of combustion of the alkyl phenyl ketones with the corresponding values for the liquid alkylbenzenes, reported by Prosen, Johnson and Rossini[1], the following conclusions can be drawn.

Table 2. Data from combustion experiments with alkyl phenyl ketones

Expt. No.	*Mass of carbon dioxide* (g)	$\Delta\varepsilon_{\text{Ag}}$ (J/Ω)	ΔR_{e} (Ω)	Q_{rxvc} (J)	q_{f} (J)	q_{n} (J)	$-\Delta E_{\text{B}}$ (28°C) (J/g of CO_2)	*Mean value* $-\Delta E_{\text{B}}$ (J/g of CO_2)
				Methyl phenyl ketone				
1	3·62191	24·4	0·302301	42728·2	63·4	2·5	11779·0	
2	3·62318	24·4	0·302359	42736·6	61·5	2·1	11777·7	11779·4
3	3·63150	24·4	0·303132	42845·8	64·2	2·4	11780·0	± 0·7
4	3·62991	24·4	0·303011	42828·6	62·4	2·4	11781·0	
				Ethyl phenyl ketone				
1	3·51073	23·4	0·301502	42615·1	62·3	2·5	12120·1	
2	3·51625	23·4	0·301935	42676·3	61·4	2·3	12118·7	12120·5
3	3·51463	23·4	0·301895	42670·6	61·9	2·9	12122·4	± 0·8
4	3·51244	23·4	0·301670	42638·8	64·0	2·1	12120·6	
				Propyl phenyl ketone				
1	3·41445	22·6	0·299881	42386·8	47·0	2·1	12399·6	
2	3·41632	22·7	0·300023	42406·9	50·3	2·1	12397·7	12400·0
3	3·41379	22·6	0·299922	42392·6	50·4	2·0	12402·7	± 1·5
				Isobutyl phenyl ketone				
1	3·33339	22·0	0·297763	42086·1	60·9	2·3	12606·7	
2	3·34221	22·0	0·298664	42213·6	61·9	2·5	12611·2	
3	3·34344	22·1	0·298686	42216·3	61·1	2·5	12607·7	12608·8
4	3·33878	22·0	0·298275	42158·5	61·2	2·4	12607·9	± 0·9
5	3·33968	22·0	0·298421	42180·5	61·5	2·3	12610·6	
				tert-Butyl phenyl ketone				
1	3·42902	22·6	0·306826	43367·2	61·7	4·2	12627·9	
2	3·42394	22·6	0·306458	43315·3	61·1	3·0	12632·0	12632·3
3	3·37080	22·2	0·301694	42641·8	61·4	3·1	12631·2	± 2·1
4	3·36889	22·2	0·301686	42640·7	62·6	2·3	12637·9	

Table 3. Heats of combustion and formation of alkyl phenyl ketones

Compound (*liq.*)	$-\Delta E_B$ 28°C (kJ/mole)	$-\Delta E^\circ$ 28°C (kJ/mole)	$-\Delta H_c^\circ$ 28°C (kJ/mole)	$-\Delta H_c^\circ$ 25°C (kJ/mole)	$-\Delta H_c^\circ$ 25°C (kcal/mole)	ΔH_f° 25°C (kcal/mole)
Methyl phenyl ketone	4147·39 ± 0·89	4144·95 ± 0·89	4148·71 ± 0·89	4148·95 ± 0·89	991·62 ± 0·21	− 34·06 ± 0·25
Ethyl phenyl ketone	4800·90 ± 1·05	4798·28 ± 1·05	4803·29 ± 1·05	4803·66 ± 1·05	1148·10 ± 0·25	− 39·95 ± 0·30
Propyl phenyl ketone	5457·36 ± 1·69	5454·66 ± 1·69	5460·83 ± 1·69	5461·32 ± 1·69	1305·29 ± 0·40	− 45·13 ± 0·45
Isobutyl phenyl ketone	6104·19 ± 1·39	6101·23 ± 1·39	6108·74 ± 1·39	6109·36 ± 1·39	1460·17 ± 0·33	− 52·62 ± 0·39
tert-Butyl phenyl ketone	6115·54 ± 2·26	6112·57 ± 2·26	6120·09 ± 2·26	6120·70 ± 2·26	1462·88 ± 0·54	− 49·91 ± 0·60

(a) The increments in the heats of combustion per CH_2 group added to the chain in the liquids methyl phenyl ketone and methylbenzene have the same value of 156·5 kcal/mole. This identity of increments in the heats of combustion per CH_2 group added to the chain is again reproduced in the liquids propyl phenyl ketone and propylbenzene with the same value of 154·9 kcal/mole.

(b) The increments in the heats of combustion per CH_2 group added to the chain in the liquids ethyl phenyl ketone and ethylbenzene have an unexpected difference of 1 kcal/mole: 157·2 kcal/mole and 156·2 kcal/mole, respectively.

(c) There is an important difference between the heats of isomerization for the liquid state at 25°C of the following reactions:

Isobutyl phenyl ketone ⟶ *tert*-Butyl phenyl ketone −2·7 kcal/mole

Isobutylbenzene ⟶ *tert*-Butyl benzene +0·2 kcal/mole

Finally, from the heat of combustion of benzyl methyl ketone, measured by Springall and Nicholson[5, 3], and our experimental results, the heat of isomerization of the following reaction for the liquid state at 25°C has been computed:

Ethyl phenyl ketone ⟶ Benzyl methyl ketone −3·6 kcal/mole

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VOL
2
1961

THERMOCHEMICAL INVESTIGATIONS ON METHYL-SUBSTITUTED BENZOIC ACIDS: I. TOLUIC ACIDS

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The thermochemical study of the methyl-substituted benzoic acids has been undertaken as a contribution to the basic thermodynamic information on pure organic compounds. This paper contains the thermochemical data of the three first members of this series: the toluic acids. The unit of energy upon which values reported in this paper are based is the absolute joule. The relation 1 cal = 4·1840 J is used. The molecular weight of carbon dioxide is taken as 44·011.

METHOD AND APPARATUS

The heats of combustion of the compounds were determined by burning the solid acids in the form of pellets in oxygen in a bomb, at constant volume. The procedure is similar to that described by Prosen[1]. The samples were weighed and placed in a platinum crucible in the bomb, 1 ml of water was added to the bomb, and the bomb was flushed and filled with purified oxygen to 30 atm pressure at 25°C. The sample was ignited by means of an iron wire fuse, 0·012 cm in diameter and 6 cm long, coiled above the sample. The amount of reaction was determined from the mass of carbon dioxide formed in the combustion. The heat of reaction was referred to the final calorimetric temperature of 28°C. Experiments with standard benzoic acid were carried out to determine the energy equivalent of the calorimetric system. A series of calorimetric combustion experiments was made with each of the three toluic acids. The same calorimetric system, platinum resistance thermometer and Mueller bridge were used for all the experiments.

A check on the completeness of reaction was afforded by the ratio, r, of carbon dioxide produced in the combustion to the stoichiometric amount of carbon dioxide calculated from the mass of toluic acid, corrected to vacuum, and its density. The density used for the three toluic acids was 1·30 g/cm^3. The average values of r were always very close to 1·0000.

Materials

The *ortho*-, *meta*- and *para*-toluic acids from British Drug Houses, Ltd (England) were purified first by vacuum sublimation and then by zone-melting, with a simple and efficient device developed in this laboratory. The qualitative control of purity of the three toluic acids, by heating curves, according to the method of Skau[2], showed that those compounds were of a high degree of purity.

EXPERIMENTAL RESULTS

The results of a series of calibration experiments using N.B.S. standard benzoic acid are given in *Table 1*, which shows the experiment number, the mass of benzoic acid burned (corrected to vacuum), the deviation, Δe_1, of the energy equivalent from that of the standard calorimeter system, the corrected temperature rise ΔR_c, the ignition energy correction q_i, the nitric acid correction q_n, the energy equivalent E_s, and the deviation from the mean.

The values of q_n were computed from the amount of nitric acid formed using the value 57·8 kJ/mole for the standard heat of formation of nitric acid from nitrogen, oxygen, and liquid water. The values of q_i were obtained from separate ignition experiments in which a standard mass of 5·60 mg of iron was burned (standard $q_i = 41{\cdot}1$ J) but are corrected to the actual mass of iron burned in each experiment using 7·5 J/mg for the heat of combustion of iron. (On the experiments Nos. 1 and 2 another iron wire was used with a standard mass of 8·30 mg of iron.) The value of Δe_1 for each experiment was computed from the heat capacity of benzoic acid taken as 1·21 J g^{-1} °C^{-1} at 26·5°C converted to J/Ω on the resistance thermometer used.

From the data in *Table 1*, the energy equivalent of the standard calorimeter system E_s is computed as follows:

$$E_s = [(-\Delta E_{B,\,28°C}\ m_s + q_i + q_n)/\Delta R_c] - \Delta e_1 \text{ J}/\Omega$$

where $-\Delta E_{B,\,28°C} = 26431{\cdot}8$ J/g is the heat of combustion of standard benzoic acid under the actual bomb conditions.

Table 1. Calibration experiments with benzoic acid

Expt No.	*Mass of benzoic acid* (g)	Δe_1 (J/Ω)	ΔR_c (Ω)	q_i (J)	q_n (J)	E_s (J/Ω)	*Deviation from mean* (J/Ω)
1	1·60272	19·2	0·300232	62·4	2·3	141296·4	− 8·9
2	1·60327	19·2	0·300306	61·5	2·6	141308·0	+ 2·7
3	1·60290	19·2	0·300089	43·2	1·7	141313·6	+ 8·3
4	1·60248	19·2	0·300042	42·0	3·0	141299·1	− 6·2
5	1·60238	19·2	0·300006	42·2	1·9	141304·3	− 1·0
6	1·60240	19·2	0·299975	42·0	1·9	141320·0	+ 14·7
7	1·60136	19·2	0·299800	41·8	2·7	141312·8	+ 7·5
8	1·60209	19·2	0·299947	42·0	2·7	141308·5	+ 3·2
9	1·60167	19·2	0·299890	42·1	2·6	141298·4	− 6·9
10	1·60260	19·2	0·300077	42·1	2·6	141292·2	− 13·1
						Mean, 141305·3	
						S.D. of mean, ± 5·6	

Table 2 lists the data for the calorimetric combustion experiments of the three toluic acids. Δe_2 is the deviation from the standard calorimetric system; $Q_{28°C} = (E_s + \Delta e_2)\Delta R_c$ is the isothermal heat liberated by the process which took place in the bomb; and $-\Delta E_{B,28°C} = Q_{,28°C} - q_i - q_n$ is the heat of combustion in the bomb process.

Table 2. Combustion experiments with toluic acids

Expt. No.	*Mass of carbon dioxide* (g)	$\Delta\varepsilon_2$ (J/Ω)	ΔR_C (Ω)	$Q_{28°C}$ (J)	q_1 (J)	q_n (J)	$-\Delta E_B$, 28°C (J/g of CO_2)	*Mean value* $-\Delta E_B$ (J/g of CO_2)
				o-Toluic acid				
1	3·80624	18·8	0·296702	41931·1	41·7	6·1	11003·9	
2	3·96951	19·6	0·309387	43724·1	40·0	6·1	11003·4	
3	3·86876	26·0	0·301652	42632·9	42·1	7·6	11006·9	11005·0
4	3·86323	26·0	0·301172	42565·0	42·8	6·5	11005·2	± 0·6
5	3·86426	26·0	0·301263	42577·9	41·9	7·3	11005·7	
				m-Toluic acid				
1	3·86434	25·3	0·300494	42469·0	42·4	6·5	10977·3	10978·1 ± 0·8
2	3·85449	25·2	0·299777	42367·6	43·0	6·8	10978·8	
3	3·89990	−17·3	0·303236	42843·6	41·8	3·4	10974·2	10975·2 ± 0·7
4	3·86532	−17·4	0·300616	42473·4	41·8	3·7	10976·6	
5	3·88144	−17·4	0·301815	42642·8	40·3	4·3	10974·8	
				p-Toluic acid				
1	3·87614	18·3	0·301220	42569·5	41·7	6·5	10970·0	
2	3·87233	18·3	0·300978	42535·3	42·1	8·8	10971·3	
3	3·87169	18·2	0·300810	42511·5	43·0	8·0	10966·9	10968·7
4	3·86532	18·2	0·300372	42449·6	42·7	8·7	10968·9	± 0·9
5	3·87671	18·3	0·301176	42563·3	42·0	8·4	10966·2	

The values of $\Delta\varepsilon_2$ were computed from the heat capacities: 12·8, 12·1 and 12·0 J g^{-1} Ω^{-1} for *o*-, *m*- and *p*-toluic acid, respectively[3], and the heat capacity of any parts of the calorimeter which were changed during the course of this investigation. Thus, in combustion experiments 3, 4 and 5 of the *o*-toluic acid and 1 and 2 of the *m*-toluic acid a transitory modification of the bomb was introduced, which is reflected in the related $\Delta\varepsilon_2$ values.

As complete combustion of the *m*-toluic acid was very difficult at the standard pressure of 30 atm, the *m*-toluic acid combustion experiments 3, 4 and 5 were performed with the bomb filled with purified oxygen to 20 atm pressure* at 25°C. This explains the difference in the $\Delta\varepsilon_2$ values and the two mean values of $-\Delta E_{B,28°C}$ for the *m*-toluic acid.

In *Table 3* the following quantities are given for each of the compounds: the mean value of $-\Delta E_{B,28°C}$, from *Table 2*, expressed in kilojoules per mole of acid; $-\Delta E^{\circ}_{28°C}$, the decrement in internal energy in the ideal bomb process; $-\Delta H^{\circ}_{c,28°C}$, the heat of combustion at constant pressure at 28°C; $-\Delta H^{\circ}_{c,25°C}$, the heat of combustion at constant pressure at 25°C; and ΔH°_{f}, the heat of formation at constant pressure at 25°C.

* The deviation from the standard calorimeter system due to the difference between 30 and 20 atm pressure of oxygen ($\Delta\varepsilon$ = 35·83 J/Ω) was computed from the volume of the bomb (0·387 l.) and the heat capacity of oxygen at constant volume taken as 20·96 J $mole^{-1}$ $°C^{-1}$ converted to J/Ω on the resistance thermometer used.

Table 3. Heats of combustion and formation of the toluic acids

Compound (cryst.)	$-\Delta E_B^\circ$, 28°C (kJ/mole)	$-\Delta E^\circ$, 28°C (kJ/mole)	$-\Delta H_C^\circ$, 28°C (kJ/mole)	$-\Delta H_C^\circ$, 25°C (kJ/mole)	$-\Delta H_C^\circ$, 25°C (kcal/mole)	ΔH_f°, 25°C (kcal/mole)
o-Toluic acid	3874·73 ± 0·77	3872·02 ± 0·77	3874·53 ± 0·77	3875·00 ± 0·77	926·14 ± 0·18	− 99·55 ± 0·22
m-Toluic acid	3865·26 ± 0·81 3864·24 ± 0·81	3862·33 ± 0·81	3864·84 ± 0·81	3865·34 ± 0·81	923·84 ± 0·19	− 101·84 ± 0·23
p-Toluic acid	3861·95 ± 0·93	3859·24 ± 0·93	3861·75 ± 0·93	3862·26 ± 0·93	923·10 ± 0·22	− 102·58 ± 0·26

The uncertainties in the heats of combustion assigned to the values in *Table 3* were calculated from the relation:

$$\text{uncertainty} = [(0{\cdot}01)^2 + (2\sigma E_s)^2 + (2\sigma\Delta E_B)^2 + (0{\cdot}01)^2]^{\frac{1}{2}}$$

where σ represents the standard deviation of the mean for the specified measurement, and all deviations are expressed as percentages of the measured quantity. The first term, 0·01 per cent, is the assigned uncertainty in the certified value of the heat of combustion of the standard benzoic acid. The second term, 0·01 per cent, is arbitrarily assigned to allow for systematic error in the measurements.

The heats of combustion refer to the reaction:

$$C_9H_8O_{2(c.)} + 9\ O_{2(g.)} = 8\ CO_{2(g.)} + 4\ H_2O_{(l.)}$$

The heats of formation refer to the reaction:

$$8\ C_{(\text{graphite})} + 4\ H_{2(g.)} + O_{2(g.)} = C_9H_8O_{2(c.)}$$

The heats of formation were calculated from the heats of combustion using the values −68·317 ± 0·010 kcal/mole for the heat of formation of liquid water and −94·052 ± 0·011 kcal/mole for the heat of formation of carbon dioxide.

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HEATS OF MIXING

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One of the most important requirements of a calorimeter for measuring the heats of mixing of liquids is the elimination of any vapour phase. For example in some of the measurements described here, in which about 1 cm^3 quantities of each liquid were mixed, a vapour space of only 1 cm^3 would have given rise to an error of 50 per cent or more in the heat of mixing.

In our previous calorimeter[1] the vapour phase was successfully eliminated but there remained a number of weak points in the design:

(1) The mercury used as confining liquid was in contact with the air so that heat exchanges with the surroundings were neither very small nor reproducible.

(2) There were rather large heat exchanges between the "mixing vessel" and the "reference vessel" caused by conduction along the thermopile between the two vessels.

(3) There was necessarily a heat effect due to breaking the glass seal which initially separated the two liquids. This effect was usually small but since no two seals were identical it was not reproducible.

(4) The quantity of mercury in the calorimeter (about 350 g), and hence the heat capacity (about 50 J/°C), were larger than desirable.

These disadvantages have been largely overcome in the new calorimeter described below. In particular:

(1) during measurements the calorimeter was completely enclosed in a vacuum jacket;
(2) a thermistor was used instead of the thermopile without loss of sensitivity but with a considerable decrease in heat losses;
(3) mixing was effected by inverting the calorimeter instead of by breaking a glass seal; and
(4) the heat capacity of the new calorimeter was about 15 J/°C.

The calorimeter was tested by making measurements on mixtures of $CCl_4 + CHCl_3$. The results agreed well with previous work[1-3], and showed a useful gain in reproducibility. For example, in our measurements of the very small heats of mixing of $CCl_2(CH_3)_2 + CCl_3(CH_3)$, the actual quantity of heat measured varied between 0·036 J and 0·074 J and was usually reproducible to within 0·001 J.

New measurements have been made on mixtures of pairs of the compounds $SiCl_n(CH_3)_{4-n}$ and of pairs of the compounds $CCl_n(CH_3)_{4-n}$. These measurements are being continued, but a preliminary account is given here of the results so far obtained. These substances were chosen because the molecules though roughly spherical in *shape* are by no means spherical in their *force fields*.

THE CALORIMETER

The calorimeter is shown in *Figure 1*. It consisted of a glass vessel with inner and outer cylindrical compartments A and B and a capillary tube C,

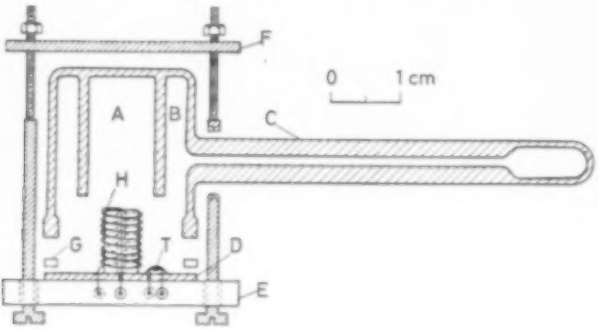

Figure 1

which could be held tightly against a flat glass plate D mounted on a Perspex plate E and carrying an electrical heating coil H and a thermistor T, any leakage being prevented by a neoprene gasket G. The heating coil H and thermistor T were cemented into place and insulated with Araldite.

The calorimeter was loaded as follows. The vessel was inverted under mercury and a thread of mercury a few centimetres long was introduced

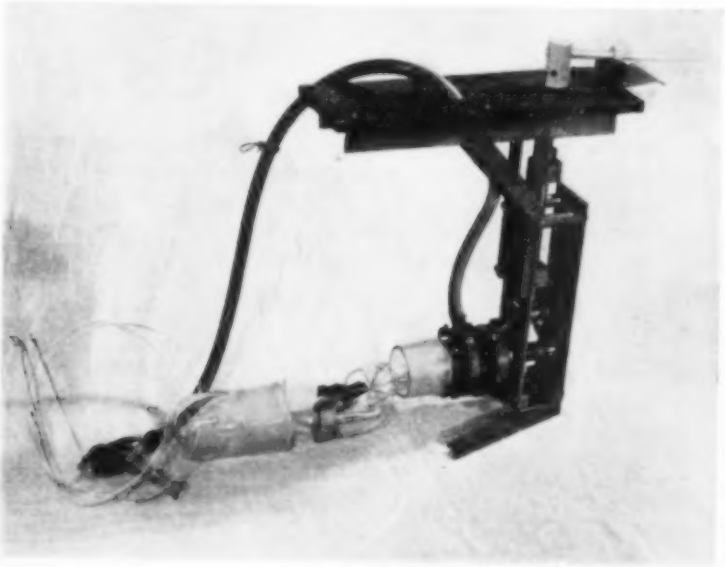

Figure 2

into C. The vessel, still under mercury, was then turned right way up. A weighed quantity (0·1 — 1·0 g) of one of the two liquids was then introduced into A by means of a hypodermic syringe with a bent needle. A weighed quantity of the other liquid was similarly introduced into B. The base plate was then carefully brought into position and the whole screwed tightly together as indicated in *Figure 1*. The loaded calorimeter was then lifted carefully (so as to prevent premature mixing) from the bowl of mercury in which these operations had been carried out and was fitted into a vacuum jacket made from a large ground-glass joint as shown in *Figures 2* and *3*. This jacket was arranged so that it could be turned over, so as to invert the calorimeter and bring about mixing, without detaching it from the vacuum line and without seriously disturbing the electrical connections from the heating coil and thermistor. The complete apparatus as shown in *Figure 3* was placed in a precision thermostat, evacuated, and left overnight to come to thermal equilibrium. The thermistor was made one arm of a Wheatstone bridge arranged so that the current passing through the thermistor was as small as possible. Since all the liquids studied absorbed heat on mixing, the heat of mixing was compensated as nearly as possible by the simultaneous liberation of a measured quantity of heat in the electrical heating coil[1].

RESULTS AND DISCUSSION

We were interested to see how far, if at all, a lattice theory allowing for preferred orientations would account for the results of mixing pairs of

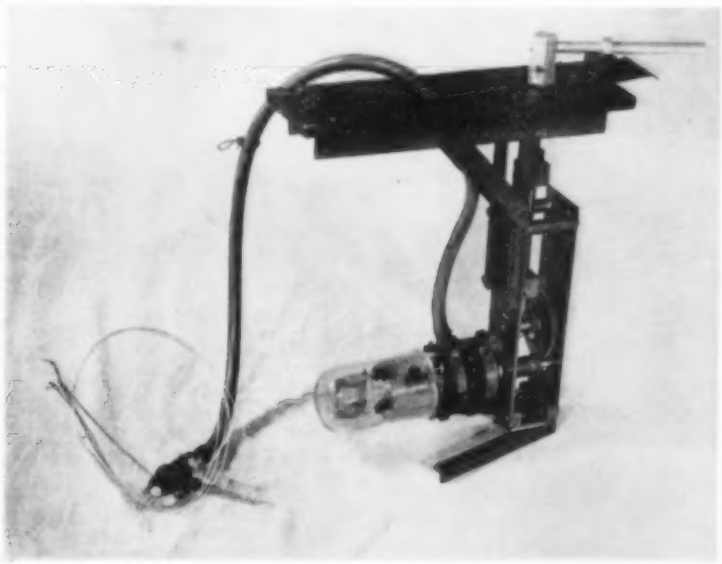

Figure 3

substances $MCl_n(CH_3)_{4-n}$ with, for given M(= Si or C), a single value for the energy of " interchange of contacts ":

$$—Cl \ldots Cl— \; + \; —CH_3 \ldots CH_3— \longrightarrow 2\,—Cl \ldots CH_3— \qquad (1)$$

Similar theories have been discussed by Münster[4], Tompa[5], Barker[6], Barker, Brown and Smith[7] and Guggenheim[8].

Let N_A, N_B molecules of A, B each occupy r_A, r_B sites on a lattice of co-ordination number z. Let $q_X z = r_X z - 2r_X + 2$ be the total number of points of contact of a molecule of type X with other molecules. Of these points of contact of a molecule X let a fraction α_X be of type a (*e.g.* Cl), and let a fraction $1 - \alpha_X$ be of type b (*e.g.* CH_3). We define a quantity γ by the relation

$$\gamma = [(1 - x)\alpha_A q_A + x\alpha_B q_B]/[(1 - x)q_A + xq_B] \qquad (2)$$

where x is the mole fraction, $N_B/(N_A + N_B)$, of substance B in the mixture. We further define an energy parameter $2u/z$ equal to the energy of the interchange of contacts shown in equation (1).

It can then be shown (for a general method see Guggenheim[8]) that the molar energy of mixing, ΔU_m, is given by

$$\Delta U_m/Lu = [(1 - x)q_A + xq_B]y(x) - (1 - x)q_A y(0) - xq_B y(1) \qquad (3)$$

with $y = y(x)$ given by the " quasi-chemical " formula

$$(\gamma - y)(1 - \gamma - y) = y^2\eta^2 \qquad (4)$$

where η^{-2} is the " equilibrium constant " of process (1) according to the

Table 1. Molar heats of mixing at 25°C

r_A	r_B	ΔH_m (J/mole) for M = Si, $x = 0{\cdot}5$		
		Exp.	Calc. for $\eta^2 = 1$, $Lu = 2160$ J/mole	Calc. for $\eta^2 = 3$, $Lu = 2510$ J/mole
2	3	38	101	73
2	4	405	405	405
3	4	140	101	148
		ΔH_m (J/mole) for M = C, $x = 0{\cdot}5$		
		Exp.	Calc. for $\eta^2 = 1$, $Lu = 710$ J/mole	Calc. for $\eta^2 = 25$, $Lu = 1570$ J/mole
2	3	6	33	16
2	4	133	133	133
3	4	103	33	70
1	2	11	33	16
1	3	2·4	133	63
1	4	49	299	212
0	4	300*	532	391

* From the measurements at 0°C of Englert-Chwoles[9].

VOL. 2 1961

quasi-chemical theory, γ is given by equation (2), and L is Avogadro's number.

To compare the theory with our experimental results we make the reasonable assumptions that $r = 5$ and $z = 4$ so that $q = 3$ throughout. Then for mixtures of $A = MCl_{n'}(CH_3)_{4-n'} + B = MCl_{n''}(CH_3)_{4-n''}$, identifying a with Cl and b with CH_3, we have $\alpha_A = n'/4$ and $\alpha_B = n''/4$.

In *Table 1* we give our experimental results for the molar heat of mixing ΔH_m at $x = 0{\cdot}5$ and 25°C for three pairs with M = Si and for seven pairs with M = C. In the third column we give values calculated from formula (3) with $\eta^2 = 1$, that is to say for the "zeroth approximation" corresponding to random mixing of contacts in spite of a finite energy of interchange. The values in the fourth column were calculated from formula (3) with $\eta^2 = 3$ for the silicon compounds, and $\eta^2 = 25$ for the carbon compounds.

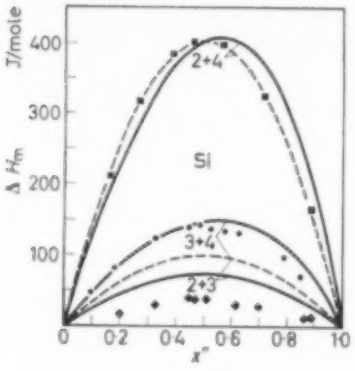

Figure 4

This is the so-called "quasi-chemical approximation" and the values chosen for η^2 imply that in the silicon compounds there is a slight preference, and in the carbon compounds a stronger preference, for contacts between like groups rather than between unlike groups. For each set of compounds the formula was fitted to the result for the mixture $(n' = 2) + (n'' = 4)$.

Dealing first with the results for M = Si we see that the zeroth approximation correctly predicts that for both Si2 + Si3 and Si3 + Si4, ΔH_m is smaller than for Si2 + Si4, but that this approximation fails to distinguish between the first two. The quasi-chemical approximation, however, correctly predicts the order, and very roughly the relative magnitudes, for all three pairs. In *Figure 4* the results are shown plotted against the mole fraction x'' of the component with the larger value of n. We see that while the zeroth approximation implies that all the curves should be symmetrical about $x = 0{\cdot}5$, which is in close agreement with experiment, the quasi-chemical approximation implies in each case a greater or lesser displacement of the maximum towards higher values of x''.

When we turn to the results for M = C we see that for the three corresponding pairs the entries in *Table 1* lead to similar conclusions as in the case of M = Si. However, in this case, as we can see in *Figure 5*, the

quasi chemical approximation not only leads to a much better prediction of the relative magnitudes but also correctly predicts displacements of the maxima in the curves from $x'' = 0{\cdot}5$.

Unfortunately, when we turn to the results of measurements with *tert*-butyl chloride as one of the components, the situation is much less satisfactory. The theory implies much bigger values for C1 + C3 and for C1 + C4 than those actually found. We propose to repeat these measurements with a new sample of *tert*-butyl chloride, and also to extend the Si

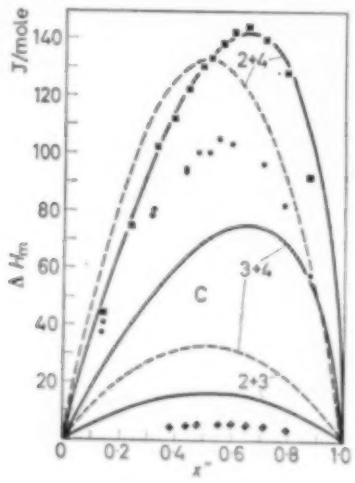

Figure 5

measurements so as to include $SiCl(CH_3)_3$ (at the moment we are worried about an apparent reaction of this substance with mercury), and $Si(CH_3)_4$. We also hope soon to begin vapour pressure measurements on some of these systems.

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VOL. 2 1961

UNTERSUCHUNGEN ÜBER DIE MISCHUNGSWÄRMEN IN DEN SYSTEMEN: ESSIGSÄURE–PYRIDIN–n-PARAFFINE

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Die Messungen von Mischungswärmen in Zwei- und Dreikomponentensystemen wurden unter Anwendung der Vergleichsmethode in Zwillingskalorimetern ausgeführt, die mit thermostatischen Mänteln versehen waren. Der Wärmewert des Bezugskalorimeters wurde auf Grund der Neutralisationswärme des Systems Salzsäure–Natronlauge bestimmt, wobei selbstverständlich die Korrekturen für die Verdünungswärme der entsprechenden Lösungen berücksichtigt wurden.

Die Bestimmungen wurden im Temperaturintervall von 20° bis 21°C durchgeführt, wovon jedoch die Mischungswärmen von Pyridin mit Essigsäure ausgenommen sind, da ihre Werte einen bedeutend grösseren Temperaturzuwachs zur Folge hatten, als 1 Grad C. Die Mengen der entsprechenden Mischungen wurden so gewählt, dass das Gesamtvolumen der Flüssigkeit in jedem Fall das gleiche war.

Die Zusammensetzung der Mischungen wurde aus den Gewichten der Komponenten berechnet. Ausserdem ist nach jeder Messung das Gesamtgewicht der Mischung kontrolliert worden. Die Komponenten waren in luftdichten Gefässen untergebracht. Bei der Konstruktion des Kalorimeters haben wir uns bemüht, einen verhältnismässig kleinen Luftraum über der Flüssigkeit einzuhalten. Um die Wärmeverluste des Kalorimeters sowie die Verdampfungswärme zu berücksichtigen, wurde bei den Berechnungen die Regnault–Pfaundler'sche Korrektur angewandt.

Jede Messung ist mindestens zweimal ausgeführt worden. Die Untersuchungen wurden so geführt, dass in einer Reihe von Bestimmungen die Komponente A zur Komponente B oder der Mischung AB gegeben wurde und in einer zweiten die Komponente B zu A oder der Mischung BA hinzugefügt wurde. Überdeckung der beiden Kurven der molaren Mischungswärmen, von denen eine von der reinen Komponente A und die zweite von der Komponente B ausging, war ein Kriterium für die Genauigkeit der erhaltenen Ergebnisse. Der Messfehler wurde auf etwa 2 Prozent geschätzt.

Eng begrenzte Fraktionen der entsprechenden Kohlenwasserstoffe wurden durch Destillation auf selektiven Destillationskolonnen erhalten. Entwässertes Pyridin und Essigsäure wurden gleichfalls einer sorgfältigen Destillation unterworfen.

Messungen der Mischungswärmen von Essigsäure mit Pyridin waren bereits im Jahre 1947 von N. A. Pušin, A. V. Fediuškin und B. Krgović ausgeführt worden[1]. Im Gegensatz zu den im allgemeinen mit unseren übereinstimmenden Ergebnissen der genannten Autoren haben wir eine

mehr ausgeprägte und stärkere Änderung der molaren Mischungswärme im Konzentrationsintervall des Maximums gefunden. Die charakteristische Gestalt der Kurve, deren Maximum bei 60 Molprozent der Essigsäure liegt, sowie der verhältnismässig grosse Wert der Wärme im Maximum, der etwa 1,16 kcal beträgt, weisen auf eine Möglichkeit der Bildung einer besonderen Konfiguration von der Zusammensetzung 2 Pyridin zu 3 Essigsäure hin. Zu einem ähnlichen Schluss, jedoch auf Grund anderer Untersuchungsmethoden, sind auch Gardner[2], Zawidzki[3] und Naumova[4] gekommen. Der Gestalt nach erinnert die Kurve der molaren Mischungswärme an sogenannte singuläre Kurven, sie scheint im Maximum zwei Tangenten zu haben.

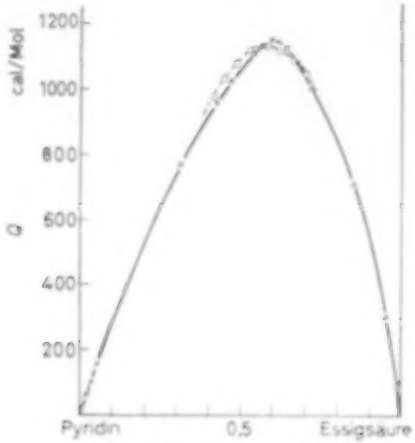

Abb. 1. —o— N. A. Pušin, A. V. Fedjuškin und B. Krgović
—×— M. Wóycicka

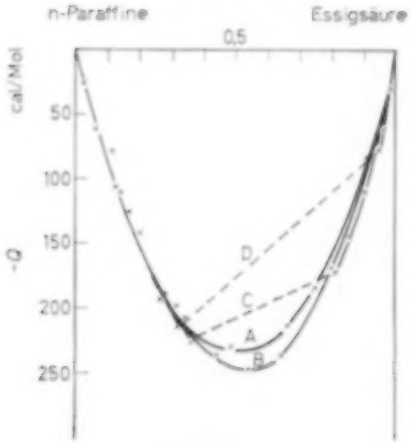

Abb. 2

A, n-Hexan: $\Delta H_{1,2} = x_1 x_2 [932-158 (x_1 - x_2) + 44(x_1 - x_2)^2]$;
B, n-Heptan: $\Delta H_{1,2} = x_1 x_2 [980-276 (x_1 - x_2) + 236 (x_1 - x_2)^2]$;
C, n-Oktan; D, n-Nonan

Messungen der molaren Mischungswärme in den Systemen Essigsäure–normale Kohlenwasserstoffe waren auf die Repräsentanten n-Hexan, n-Heptan, n-Oktan und n-Nonan beschränkt. Der Grund dafür lag in der Tatsache, dass vom n-Oktan beginnend eine Mischungslücke auftritt. Dennoch wurden die Messungen auch für n-Oktan und n-Nonan ausgeführt, jedoch nur im Konzentrationsintervall der Homogenität.

Trotz der Anwesenheit einer Mischungslücke in den genannten Fällen konnte festgestellt werden, dass innerhalb der Messfehlergrenzen eine Überdeckung der Kurven der molaren Mischungswärmen im Konzentrationsintervall von 0 bis 30 Molprozent Essigsäure auftritt. Diese Tatsache zeugt davon, dass die Mischungswärme eines Mols Essigsäure mit einer im Grenzwert unendlich grossen Menge des Kohlenwasserstoffs einen konstanten Wert von etwa $-0{,}99 \pm 0{,}04$ kcal/Mol aufweist, der unabhängig ist von dem untersuchten Repräsentanten der Kohlenwasserstoffhomologe.

Die Mischungswärme betrug im Minimum bei n-Hexan -237 cal/Mol und bei n-Heptan -247 cal/Mol. Infolge der erwähnten Mischungslücke ist es schwierig zu beurteilen, inwiefern dieser Wert bei weiteren Kohlenwasserstoffen sich regulär verändern wird.

Die hierbei festgestellte Verschiebung des Minimums in Richtung zur polaren Komponente kann nicht durch Messfehler bedingt sein und sie tritt bei den Systemen Pyridin–Kohlewasserstoff noch deutlicher auf.

Trotz der Anwesenheit eines polaren Bestandteils in den untersuchten Mischungen konnte der Verlauf der experimentellen Ergebnisse mittels der von Redlich und Kister[5] sowie Scatchard und Ticknor[6] benutzten Interpolationsformel

$$\Delta H_{1,2} = x_1 x_2[A_0 + A_1(x_1 - x_2) + A_2(x_1 - x_2)^2 + \ldots.]$$

in allen Fällen recht gut approximiert werden, wobei zumeist die Anwendung der ersten drei Glieder bereits zufriedenstellende Ergebnisse lieferte.

Gewisse Gesetzlichkeiten im Verlauf der molaren Mischungswärmen, die in den Systemen n-Paraffine–Essigsäure erfasst worden sind, treten noch deutlicher auf beim Übergang zur Systemgruppe n-Paraffine–Pyridin (*Abb. 3*). Die Minimalwerte (von -390 bei Hexan bis -492 cal/Mol bei Undekan) verändern sich regulär um etwa 10 cal/Mol beim Übergang von einem zum nächsten Vertreter der Paraffinreihe von n-Heptan bis n-Dekan, was zur Folge hat, dass die Konstante A_0 in der erwähnten Gleichung für $\Delta H_{1,2}$ einen steten Zuwachs von etwa 40 cal/Mol erfährt. Grössere Abweichungen von dieser Gesetzlichkeit treten bei n-Hexan auf. Der Grund dafür kann in einem beträchtlicheren Messfehler gesucht werden, der in diesem Fall fast 5 Prozent beträgt und durch die hohe Flüchtigkeit dieses Wasserstoffs in der Messungstemperatur verursacht ist.

Die lage derjenigen Mischungszusammensetzungen, bei denen das Minimum auftritt, erfährt eine geringe, aber deutlich erkennbare Verschiebung in der Richtung zum polaren Bestandteil—Pyridin.

Ähnlich wie bei der Systemgruppe n-Paraffine–Essigsäure kann auch in der zweiten Mischungsgruppe: n-Paraffine–Pyridin eine Überdeckung der Kurven bei geringen Pyridin-Konzentrationen von 0 bis etwa 15 Molprozent festgestellt werden. Der ermittelte Grenzwert der Mischungswärme

von einen Mol Pyridin in einer unendlich grossen Menge eines beliebigen Kohlenwasserstoffs der untersuchten Reihe beträgt $-2{,}10 \pm 0{,}08$ kcal/Mol.

Die angeführten Ergebnisse stehen kaum im Einklang mit Andeutungen, die aus den Untersuchungen von Hildebrand zu folgen scheinen. Laut diesen Arbeiten müssen die Mischungswärmen einen angenähert konstanten Wert für alle Vertreter der homologen Reihe haben.

Untersuchungen der Systeme von drei Komponenten wurden in den Fällen Essigsäure–Pyridin–n-Hexan bezw. n-Heptan durchgeführt.

Die Diskussion der dabei erhaltenen Ergebnisse erfordert eine Anwendung von räumlichen Vorstellungen. Wir denken uns also die Zusammensetzungskoordinaten durch das Gibbs'sche Dreieck bestimmt und die ihnen entsprechenden Werte der Mischungswärmen als senkrecht zur Ebene des Dreiecks aufgetragen. Die Gesamtmenge der so erhaltenen Punkte bestimmt eine Fläche, deren Gestalt durch die Werte sowie durch das Vorzeichen der Effekte bedingt ist, die bei den Zweikomponenten-Systemen auftreten. Projektion der Kurven gleicher Mischungswärmen auf das Gibbs'sche Dreieck ergiebt das topographische Bild dieser Fläche.

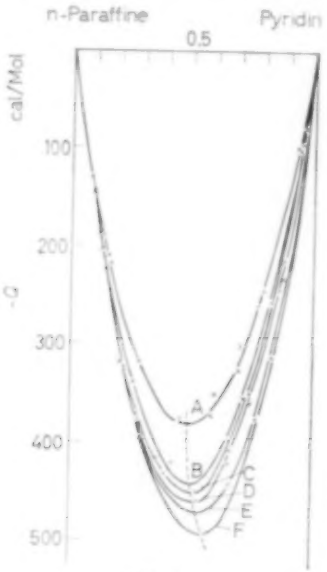

Abb. 3

A, n-Hexan: $H_{1,2} = x_1 x_2 [1520 + 71 (x_1 - x_2) + 96(x_1 - x_2)^2]$
B, n-Heptan: $H_{1,2} = x_1 x_2 [1760 - 66 (x_1 - x_2)]$
C, n-Oktan: $H_{1,2} = x_1 x_2 [1800 + 74 (x_1 - x_2) + 405 (x_1 - x_2)^2]$
D, n-Nonan: $H_{1,2} = x_1 x_2 [1840 + 67 (x_1 - x_2)]$
E, n-Dekan: $H_{1,2} = x_1 x_2 [1880 + 210 (x_1 - x_2) + 384 (x_1 - x_2)^2]$
F, n-Undekan: $H_{1,2} = x_1 x_2 [1960 - 289 (x_1 - x_2) + 345 (x_1 - x_2)^2]$

In jeder Messreihe wurde zur vorbereiteten Mischung von zwei Komponenten die reine dritte Komponente hinzugegeben. Die entsprechenden Zusammensetzungen der im Ergebnis erhaltenen Mischungen wurden so gewählt, dass sie auf Geraden lagen, die parallel zu der Geraden verlaufen die Essigsäure mit Pyridin im Gibbs'schen Dreieck verbindet. Dieses

VOL. 2 1961

Verfahren ermöglichte es, nach einer rechnerischen Bearbeitung der Messergebnisse eine Reihe von Querschnitten zu erhalten, auf denen sich die Gestalt der Kurven der Mischungswärme deutlich erkennen liess.

Für jedes System wurden etwa 60 Messungen ausgeführt. Obwohl die binären Gemische, die aus Essigsäure, Pyridin–n-Hexan und n-Heptan gebildet werden können, in der Temperatur, bei welcher gearbeitet wurde, homogen sind, wurde bei den zwei untersuchten ternären Mischungen eine im Innern des Konzentrationsdreiecks sich befindende geschlossene Mischungslücke festgestellt. Sie wurde für die beiden Systeme in einer speziellen Untersuchung bestimmt.

Auf Grund des Verlaufs von molaren Mischungswärmen der binären Gemische konnte vorausgesehen werden, dass die Fläche der Wärmen im ternären System in zwei Gebiete zerlegt wird, von denen das eine alle exothermen und das andere alle endothermen Mischungen umfasst. Die Trennungslinie zwischen diesen Gebieten wird vom Autor als " athermale Linie " bezeichnet. Sie entspricht denjenigen Zusammensetzungen, für welche die Mischungswärme zu Null tendiert.

Eine andere charakteristische Linie wird durch die Punktmenge bestimmt, deren Vertreter maximalen Mischungswärmen auf den Querschnitten entsprechen, die parallel zum System Pyridin–Essigsäure verlaufen. Geometrisch verhält sie sich ähnlich wie die sogenannte Scheitellinie, die auf der Fläche der Siedetemperaturen von Sattelazeotropen definiert ist.

Die Scheitellinie der Mischungswärmen beginnt im Maximum des Systems Pyridin–Essigsäure und verläuft in einem leicht gekrümmten Bogen durch das exotherme Gebiet bis zur Mischungslücke (*Abb. 4*). Von der anderen Seite aus der Lücke tretend durchkreuzt sie die athermale Linie und endet schliesslich im Punkt, der dem reinen n-Hexan entspricht. Es wurde festgestellt, dass die Scheittellinie ein eigenes Minimum im Punkt A hat, für den die Mischungswärme —18 cal/Mol beträgt und dessen Koordinaten der Zusammensetzung 0,92 n-Hexan, 0,04 Pyridin, 0,04 Essigsäure entsprechen.

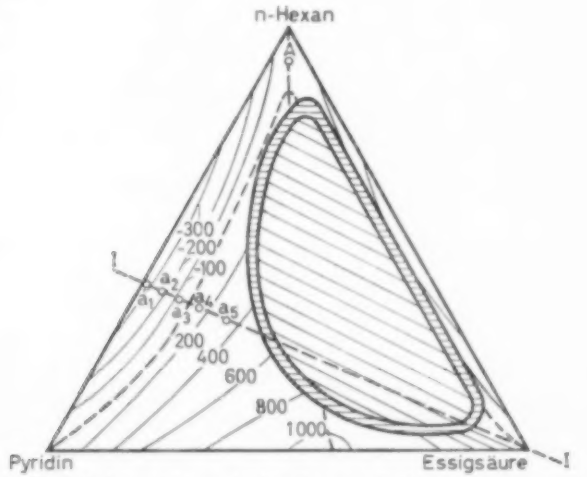

Abb. 4. Die Mischungswärmen in dem System: Pyridin–Essigsäure–n-Hexan.

Die Anwendbarkeit der von C. C. Tsa'o und J. M. Smith angegebenen Formel für Mischungswärmen[7]

$$\Delta H_{1,2,3} = \frac{x_2}{x_2 + x_3}\Delta H_{1,2} + \frac{x_2}{x_2 + x_3}\Delta H_{1,3} + (1 - x_1)\Delta H_{2,3}$$

wurde geprüft. Eine Übereinstimmung zwischen den berechneten und experimentellen Werten wurde nicht festgestellt. Sie betragen z.B. für den Querschnitt I–I (*Abb. 4*):

Zusammensetzung	a_1	a_2	a_3	a_4	a_5
$-\Delta H$ berechnet	− 311	− 174	− 82	4	170
$-\Delta H$ gemessen	− 307	− 154	− 10	120	340

Das gleichfalls untersuchte ternäre System Essigsäure–Pyridin–n-Heptan weist eine gewisse Ähnlichkeit mit dem bereits besprochenen auf in Bezug auf die charakteristischen Linien (*Abb. 5*). Die der Untersuchung zugängliche Fläche ist hier noch kleiner infolge der Ausbreitung der Mischungslücke. Der Betrag des Minimums auf der Scheitellinie im A–Punkt war −20 cal/Mol, seine Zusammensetzungskoordinaten 0,91 n-Heptan, 0,05 Pyridin und 0,04 Essigsäure.

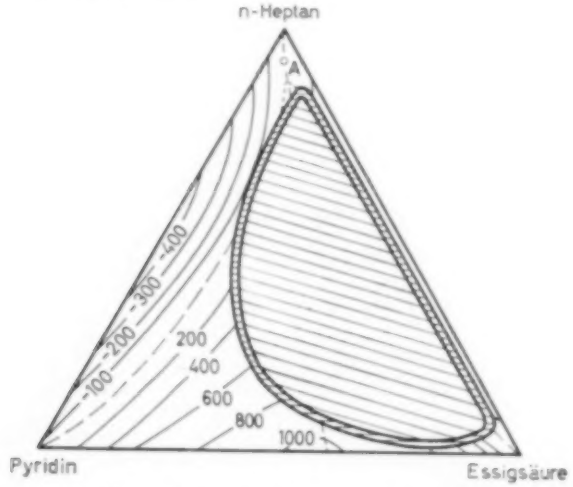

Abb. 5. Die Mischungswärmen in dem System: Pyridin–Essigsäure–n-Heptan

Die Ergebnisse der besprochenen Arbeit wurden in den unter der Leitung von W. Świętosławski ausgeführten theoretischen Untersuchungen ausgenützt, die eine Klärung der Erscheinung der Sattelazeotrope zum Ziel hatten.

In weiterer Fortsetzung der thermochemischen Untersuchungen über flüssige binäre und ternäre Gemische wird eine Arbeit über spezifische Wärmen von Mischungen Pyridin–Essigsäure–n-Paraffine bald zum Abschluss gelangen.

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VOL
2
1961

PRESENT STATUS OF THE VALUES OF THE FUNDAMENTAL CONSTANTS FOR PHYSICAL CHEMISTRY

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SUMMARY

The present status of the values of the fundamental constants for physical chemistry was presented. Since the report issued by the National Research Council Sub-committee on Fundamental Constants in 1951, the following changes have occurred: the value for the absolute temperature of the ice point (or for the triple point) of water has become a defined constant by action of the appropriate international group; improved values for the Faraday, Avogadro number, electronic charge, velocity of light, and Planck's constant have become available through some new experimental data and analysis of all the data by Dumond and Cohen. In addition, it appears that final international action may be concluded in 1961 leading to a new scale of atomic weights, based on carbon-12 equal to 12·0000. This scale, which will be the same for both chemists and physicists, will differ from the present chemist's scale by 42 parts per million and from the present physicist's scale by 317 parts per million. The change in the scale of atomic weights has the effect of further changing the value of the Avogadro number (and, correspondingly, the pressure–volume product for one mole of ideal gas). The simultaneous lowering of the value of the absolute temperature of the ice point (by 37 parts per million) and of the value of the pressure–volume product for one mole of ideal gas (by 42 parts per million) almost cancels their effect on the value of the molar gas constant, which will change only by about 5 parts per million. Appropriate details of the foregoing matters were given.

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VOL
2
1961

DIE THERMODYNAMISCHE TEMPERATURSKALA UND IHRE REALISIERUNG UNTERHALB 90°K

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EINFÜHRUNG

Die Temperaturmessungen unterhalb 90°K schliessen sich hauptsächlich in vier Weisen an die thermodynamische Temperaturskala an:

(a) durch Messungen mit einem Gasthermometer;
(b) mit Hilfe einer thermodynamischen Beziehung für den Sättigungsdruck eines verflüssigten Gases;
(c) durch Benutzung des Gesetzes von Curie oder von Curie–Weiss für paramagnetische Salze;
(d) unter Zuhilfenahme eines umkehrbaren Kreisprozesses.

Gasthermometrische Messungen

Messungen mit Gasthermometern sind vielfach zu folgenden Zwecken benutzt worden:

(a) zur Bestimmung von Fixpunkten (Siedepunkte, Tripelpunkte, Transformationspunkte);
(b) zur Messung von Sättigungsdrucken kondensierter Gase;
(c) zur Eichung von Sekundärthermometern;
(d) schliesslich wird das Gasthermometer manchmal wie ein Interpolationsthermometer benutzt.

HAUPTFIXPUNKTE

Die wichtigsten Fixpunkte für das Gebiet der niedrigen Temperaturen sind die Siedepunkte von Sauerstoff, Wasserstoff und Helium. In *Tabelle 1* sind die Ergebnisse von den genauesten Arbeiten zusammengestellt. Die Tabelle gibt das Ergebnis einer konsistenten Neuberechnung.

In der Internationalen Temperaturskala hat der Siedepunkt des Sauerstoffes den Wert −182,97°C. Diesen hat man 1927 angenommen und er stimmt noch immer bis auf 0,01°C überein mit dem Wert, den wir heute diesem Punkt zuordnen würden. Da die Temperatur des Eispunktes 1954 auf 273,15°K festgesetzt worden ist, muss man in der Internationalen Kelvin-Skala dem Siedepunkt von Sauerstoff den Wert 90,18°K geben.

Der in *Tabelle 1* gegebene und in thermodynamisch konsistenter Weise berechnete Wert für den Siedepunkt des normalen Wasserstoffs ist fast genau gleich dem Mittelwert der von verschiedenen Instituten empfohlenen Werte, wie es *Tabelle 2* zeigt.

Die Neuberechnung des Siedepunktes von Helium hat ein Resultat gegeben, das sich nur um 0,001°K von dem von Schmidt und Keesom 1937 empfohlenen Wert unterscheidet. Der Wert 4,215°K ist in der Definition der T_{58}-Skala für Temperaturen zwischen 1,0 und 5,2°K benutzt worden.

Tabelle 1. Die normalen Siedepunkte*

		T_S (°K)	T_B (°K)
Sauerstoff			
P.T.R. 1931–32	Heuse und Otto	90,191	273,15
Leiden 1940	Frl. Van der Horst	90,160	273,15
Japan 1935	Aoyama und Kanda†	90,170	273,15
P.S.U. 1953	Aston und Moessen	90,150	273,15
	Mittelwert	90,168	
Wasserstoff			
P.T.R. 1931	Heuse und Otto	20,381	273,15
Leiden 1931	Keesom, Bijl, V. d. Horst	20,382	273,15
N.B.S. 1939	Hoge und Brickwedde	20,384	90,168
P.S.U. 1951	Moessen und Aston	20,370	273,15 1×
			90,168 2×
U.S.S.R. 1952	Borovik-Romanow und Strelkow	20,375	90,168
	Mittelwert	20,378	
Helium			
1913	Kamerlingh Onnes und Weber	4,216	273,15
1937	Schmidt und Keesom	$4,215_4$	20,378
1954	Berman und Swenson	4,215	20,378
1955	Isothermen von Keller	4,215	
	Mittelwert	4,215	

* Die normalen Siedepunkte des normalen Sauerstoffs, Wasserstoffs und Heliums sind in konsistenter Weise hergeleitet aus den ursprünglichen Messungen. Es ist für die Temperatur des Eispunktes der Wert 273,15°K genommen, für den Druckkoeffizient die Beziehung $\alpha_{0,0} = 0{,}0036099 - 0{,}32 \times 10^{-4}\, p_0$ (cm Hg) benutzt, und $T - T_{0,0}$ mit der Tabelle von W. H. Keesom berechnet worden. T_0 ist die Bezugstemperatur.

† Wasserstoffgasthermometer.

Tabelle 2. Der Siedepunkt des normalen Wasserstoffs

		T_S (°K)	T_B (°K)
P.T.R. 1931	Procès Verbaux C.I.P.M. 1952, T 60	20,38	273,16
K.O.L. 1931	Procès Verbaux C.I.P.M. 1952, T 45	20,382	273,15
N.B.S. 1939	*J. Research N.B.S.*, **22**, 351 (1939)	20,39	90 19
P.S.U. 1951	*J. Chem. Phys.* **22**, 2096 (1954)	20,365	273,16 und 90,154
I.M. 1951	Procès Verbaux C.I.P.M. 1952, T_{21} und T_{26}	20,380	
	Mittelwert	20,379	

Aus dem Vorhergehenden ist deutlich, dass die wichtigsten Fixpunkte für die Temperaturmessung unterhalb 90°K heute mit einer für die jetzige Praxis hinlänglichen Genauigkeit bekannt sind.

SEKUNDÄRE FIXPUNKTE

Die wichtigsten sekundären Fixpunkte sind der Siedepunkt von N_2, die Tripelpunkte von Argon, Sauerstoff und normalem Wasserstoff, der Siedepunkt und der Tripelpunkt von Parawasserstoff und der λ-Punkt von Helium. Die Zahlenwerte dieser Fixpunkte sind in *Tabelle 3* zusammengestellt worden.

Nicht alle sekundären Fixpunkte sind unmittelbar mit einem Gasthermometer gemessen worden.

VOL. 2 1961

Tabelle 3. Sekundäre Fixpunkte (°K)

Argon	Siedepunkt	83,81
Stickstoff	Siedepunkt	77,35
Sauerstoff	Tripelpunkt	54,34
Parawasserstoff	Siedepunkt	20,27
normaler Wasserstoff	Tripelpunkt	13,95
Parawasserstoff	Tripelpunkt	13,81
Helium	λ-Punkt	2,172

Zur genauen gasthermometrischen Bestimmung der Fixpunkte braucht man die Virialkoeffizienten des benutzten Gases. Die diesbezüglichen Korrektionen sind für das normale Heliumgasthermometer von Heuse und Otto, Keesom und Tuyn und von Keyes berechnet worden. Die Ergebnisse dieser Autoren unterscheiden sich nur um einige wenige tausendstel Grade.

DIE BENUTZUNG DES SÄTTIGUNGSDRUCKES FÜR TEMPERATURMESSUNGEN

Niedrige Temperaturen werden fast immer mit verflüssigten Gasen hergestellt. Da nun der Sättigungsdruck eine eindeutige Funktion der Temperatur darstellt, wird er sehr häufig zur Temperaturmessung benutzt, nachdem vorher die Temperaturabhängigkeit mit einem Gasthermometer gemessen worden ist. Die Sättigungsdrucke von O_2, N_2, H_2, He und von anderen weniger verwendeten Gasen sind an verschiedenen Instituten gemessen worden.

Zur Zeit ist die p–T-Beziehung für ^{4}He genau bekannt und die darauf bezogene T_{58}-Skala für das ^{4}He Gebiet ist international anerkannt worden.

Die thermodynamische p–T-Beziehung von ^{4}He und ^{3}He ist sehr wichtig für die Temperatur-Skala, weil der Dampfdruck für hinreichend niedrige Werte in einer einfachen Beziehung zur Temperatur steht. Für Drucke bis zu etwa 1 atm können Korrektionen noch mit guter Genauigkeit berechnet werden.

Für O_2, N_2 und H_2 sind von verschiedenen Autoren Daten für die Sättigungsdrucke publiziert worden. Es gibt aber keine international anerkannte p–T-Relationen für diese Gase. Nur ist für O_2, bei der Definition der internationalen Temperaturskala von 1948, eine Interpolationsformel für Drucke zwischen 660 und 860 mm Hg empfohlen worden. Im allgemeinen ist bei der Wahl einer p–T-Relation sehr zu empfehlen, nicht nur den gasthermometrischen Daten, sondern auch den thermodynamischen Daten Rechnung zu tragen und sich den thermodynamischen Formeln möglichst genau anzuschliessen. Die verschiedenen p–T-Relationen für O_2, N_2 und H_2 weisen Differenzen bis zu einigen hunderdstel Graden auf, und es ist immer noch wünschenswert, genauere Daten für diese Beziehungen zu gewinnen.

DIE THERMODYNAMISCHE TEMPERATUR UND DAS GESETZ VON CURIE-WEISS

Das Gesetz von Curie–Weiss, $\chi = C/(T - \Delta)$, enthält zwei Konstante C und Δ. In einfachen Fällen ist Δ gleich Null oder kann Δ berechnet werden. Man braucht dann nur das Verhältnis zweier Suszeptibilitäten

zu messen, um das Verhältnis der Temperaturen zu bekommen. Allerdings misst man gewöhnlich nicht χ, sondern eine lineare Funktion der Suszeptibilität:

$$m = m_0 + a\chi$$

und berechnet die sogenannte magnetische Temperatur, T_m, mit Hilfe der Beziehung:

$$T_m = \frac{A}{m - m_0} + \Delta$$

Hinlängliche Genauigkeit erhält man in der Praxis mit dieser Methode der Temperaturmessung nur bei niedrigen Temperaturen. Für Temperaturen unterhalb 1°K ist sie aber die meist benutzte Methode. Allerdings hat man dann häufig Abweichungen von einfachen Curie–Weiss-Gesetz wegen Auftretens von inneren elektrischen und magnetischen Feldern zu berücksichtigen.

Für die genaue Bestimmung der p–T-Relationen von ^{4}He und ^{3}He haben Messungen an paramagnetischen Salzen sehr wichtige Auskunft gegeben.

DER UMKEHRBARE KREISPROZESS

Die Temperaturmessung unterhalb 1°K ruht nur teilweise auf Suszeptibilitätsmessungen an Salzen. Temperaturen nahezu gleich oder kleiner als Δ können nicht mehr genau aus den gemessenen Suszeptibilitäten berechnet werden. Man kann dann einen reversiblen Kreisprozess benutzen. Führt man durch passende Änderungen der magnetischen Feldstärke und der Temperatur das paramagnetische Salz einen ganzen Kreis herum, dann ist die Entropie des Salzes am Ende dieselbe wie am Anfang:

$$\Sigma \frac{\mathrm{d}Q}{T} = 0$$

Es ist üblich, den Kreisprozess auf zwei nebeneinander liegenden Adiabaten ablaufen zu lassen. An den Endpunkten geht man von der einen auf die andere über durch eine geringe Wärmezufuhr oder -abfuhr. Es soll dann

$$\Delta S_a = \frac{\Delta Q_a}{T_a} = \frac{|\Delta Q_e|}{T_e}$$

sein, und wenn Anfangstemperatur T_a und Wärmemengen Q_a und Q_e gemessen sind, kann die Endtemperatur T_e berechnet werden. Oft genügt es, nur eine Wärmemenge zu messen. Die Entropiedifferenz ΔS_a im magnetischen Felde lässt sich dann genügend genau berechnen, und es ist

$$T_e = \frac{|\Delta Q_e|}{\Delta S_a}$$

Ist die spezifische Wärme im Magnetfeld für T_a und ohne Magnetfeld für T_e schon gemessen, dann kann die folgende Beziehung benutzt werden:

$$T_0 = T_H \frac{C_0^*}{C_H} \cdot \frac{\mathrm{d}T_0^*}{\mathrm{d}T_H}$$

VOL. 2 1961

Die spezifische Wärme C_0^* und die Temperatur T_0^* am Endpunkt auf der Adiabate können wie Funktionen eines willkürlichen Parameters gemessen werden. Am häufigsten benutzt man dafür wieder die Suszeptibilität.

SEKUNDÄRTHERMOMETER

Die thermodynamischen Temperaturen werden vielfach mit guter Genauigkeit mit Sekundärthermometern gemessen, die vorher mit Gasthermometern verglichen werden. Die wichtigsten Sekundärthermometer sind Dampfdruckthermometer, Thermoelement, Widerstandsthermometer und Halbleiterthermometer.

(a) Mit Hilfe von Dampfdruckthermometern sind viele Fixpunkte gemessen worden. Die meisten Eichungen an Widerstands- und Halbleiterthermometern werden damit vorgenommen. Bei ganz reinen Gasen wie verflüssigtes He und H_2 misst man den Dampfdruck gewöhnlich unmittelbar am Kryostaten, wiewohl für ganz genaue Messungen die Benutzung spezieller Dampfdruckthermometer zu empfehlen ist, ausgenommen wenn es sich um ^{4}He unterhalb des λ-Punktes handelt.

(b) Das mit dem Gasthermometer geeichte Thermoelement ist ebenfalls häufig für die Bestimmung von Fixpunkten und für Temperaturmessungen zwischen 90° und 10°K verwendet worden. Es hat die bekannten Vorteile der geringen Wärmekapazität und des ganz geringen Volumens. Im allgemeinen sind aber die Messungen mit einem Thermoelement weniger genau als die mit einem Widerstandsthermometer.

(c) Die für die Temperaturmessungen zwischen 90° und 10°K meistens gebrauchten und zu empfehlenden Widerstandsthermometer benutzen die Temperaturabhängigkeit des elektrischen Widerstandes von Pt, Au oder In. Am besten erforscht ist der Widerstand von fast reinem Platin. Die RT-Beziehung ist jedenfalls zwischen 90° und 10°K genügend genau bekannt für Erweiterung der internationalen Temperaturskala bis 20°K, vielleicht selbst bis 10°K. Platinthermometer höchster Reinheit stimmen zwischen 90° und 20°K in ihren Temperaturanzeigen auf einige wenige tausendstel Grad überein, wenn sie ausser am Siedepunkt des Sauerstoffs und des Wasserstoffs auch am Tripelpunkt des Sauerstoffs geeicht sind und man auf geeignete Weise interpoliert.

(d) Temperaturen in dem Temperaturgebiet von flüssigem Helium lassen sich durch Widerstandsänderungen reiner Metalle nicht messen. Einige wenige Halbleiter wie Germanium und auch manche für Radiotechnik käufliche Kohlewiderstände haben hier einen ganz erheblichen negativen Temperaturkoeffizienten. Besonders bei speziellen Germaniumproben mit einem gewissen Indiumgehalt hat man eine stärke Temperaturabhängigkeit zwischen 1° und 5°K und eine gute Reproduzierbarkeit gefunden.

(e) Eine fast lineare Temperaturabhängigkeit findet man bei vielen Phosphorbronzethermometern. Ihre Temperaturabhängigkeit verdanken sie der allmählichen Zunahme von ganz dünnen supraleitenden Fäden aus Blei oder Bleilegierungen im Innern der Bronze.

Dazu möchte ich einige erläuterende Bemerkungen machen.

(1) Für Messungen unterhalb 1°K ist die Benutzung des reversiblen Kreisprozesses sehr wichtig. Man lässt ein paramagnetisches Salz einen Kreisprozess durchlaufen, der folgendermassen dargestellt werden kann:

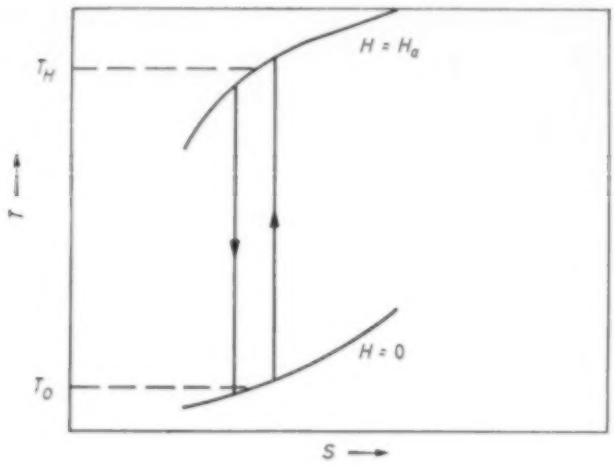

Abb. 1

Hauptsächlich geht der Weg zwei eng nebeneinander liegenden Adiabaten entlang, an deren Enden man durch Wärmezufuhr oder Wärmeabfuhr von der einen auf die andere übergeht. In der Praxis misst man nur zugeführte Wärmemengen in Abhängigkeit eines zweckmässig gewählten Parameters und korreliert die für Feld H und Feld Null gefundenen Werte des Parameters durch Demagnetisierungen und Magnetisierungen nach dem in *Abb. 2* angegebenen Schema.

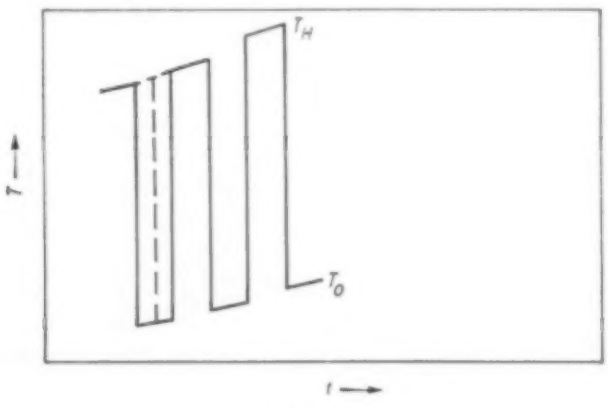

Abb. 2

VOL. 2 1961

Wichtig ist, in welcher Weise bei Feld Null die Energie zugeführt und die Temperatur gemessen wird. Im allgemeinen ist es vorteilhaft, die Energie gleichmässig allen Teilen des Salzes zuzuführen. Man kann das z.B. mit γ-Strahlen machen. Führt man die Energie an der Oberfläche zu, dann wird die Temperatur günstig durch Suszeptibilitätsmessungen bestimmt. Die gesuchte Temperatur lässt sich berechnen mit der Formel:

$$T_0 = T_H \frac{C_0^*}{C_H} \cdot \frac{\mathrm{d}T_0^*}{\mathrm{d}T_H}$$

(2) Die thermodynamische Dampfdruckformel für den Sättigungsdruck des Heliums kann geschrieben werden:

$$\ln p = i - \frac{L_0}{RT} + \frac{5}{2} \ln T - \frac{1}{RT} \int_0^T S_\mathrm{L} \, \mathrm{d}T + \frac{1}{RT} \int_0^p V_\mathrm{L} \, \mathrm{d}p + \epsilon$$

$$\text{mit } \epsilon = \ln \frac{pV_\mathrm{G}}{RT} - \frac{2B}{V_\mathrm{G}} - \frac{3C_2}{2V_\mathrm{G}}$$

Die ersten drei Terme sind die Hauptterme, die letzten drei sind Korrektionen, die allerdings bei höheren Temperaturen einen ganz beträchtlichen Einfluss haben, aber bei 1,5°K noch so klein sind, dass sich die Formel praktisch auf die ersten drei Termen reduziert. Zur Berechnung der p–T-Relation braucht man dann nur L_0 experimentell zu bestimmen, weil die statistische Thermodynamik nur mit Hilfe von genau bekannten Konstanten imstande ist, i genau zu berechnen. Zur Berechnung von L_0 braucht man nur eine gute gasthermometrische Temperaturbestimmung durchzuführen, die zu einem bestimmten Sättigungsdruck unterhalb 1,5°K gehört. Eine andere Möglichkeit zur Bestimmung von L_0 oder zur Prüfung des schon gefundenen Wertes hat man, wenn die latente Wärme des verdampfenden Heliums für niedrige Temperaturen schon gemessen ist, weil in erster Näherung $L = L_0 + (5/2)RT$. Auf diese Weise wurde von Verschaffelt ein Wert für L_0 berechnet und eine Dampfdruckformel für $T < 1{,}475$°K aufgestellt, die ein Teil der 1924-Skala war und sich von den heutigen Skalen für $T < 1{,}475$ nur um einen sehr kleinen Betrag unterscheidet.

Die Korrektionsterme der allgemeinen Dampfdruckformel können heute bis 4,2°K so genau berechnet werden, dass man eine p–T-Beziehung bekommt, die die Temperatur bis auf wenige Tausendstel Grad richtig angibt.

Eine noch genauere p–T-Beziehung bekommt man, wenn man bis 2,2°K die thermodynamische Berechnung und für Temperaturen von 2,2° bis 5,2°K die Ergebnisse von Messungen an paramagnetischen Salzen benutzt.

Die Kombination der mit beiden Methoden gewonnenen Ergebnisse lässt auch eine genauere Bestimmung von L_0 (59,62 J/Mol) zu, als es allein mit gasthermometrischen Messungen möglich ist. Auch macht diese Kombination es möglich, die Temperatur des λ-Punktes (2,172°K) mit Hilfe der schon bekannten Werte für die Siedepunkte von H_2 und He bis auf 0,001°K genau zu berechnen, weil auch der Dampfdruck am λ-Punkt

(37,80 mm Hg 0°C) genau bekannt ist. Man findet dies genauer beschrieben in *Physica 24*, 920–930 (1958).

(3) Zur Berechnung einer thermodynamischen Dampfdruckformel für den normalen Wasserstoff kann die Gleichung von Clapeyron benutzt werden:

$$\frac{\mathrm{d}p}{\mathrm{d}T} = \frac{L}{T(V_G - V_L)}$$

Unter Zuhilfenahme von aus früheren Messungen bekannten Temperaturabhängigkeiten von L, V_G und V_L lässt sich durch Integration eine Näherungsformel für die p–T-Beziehung des normalen Wasserstoffs ableiten, die der Form nach einer von Woolley, Scott und Brickwedde zur Interpolation ihrer Messresultate benutzten Formel genau entspricht.

Die Zahlenwerte der Koeffizienten in beiden Formeln weichen nur wenig von einander ab.

Keesom, Bijl und Van der Horst haben ihre mit einem Gasthermometer gewonnenen p–T-Daten des normalen Wasserstoffs mit einer T–p-Beziehung dargestellt, die sich von der thermodynamischen Beschreibung entfernt. Der Unterschied der von beiden Formeln beschriebenen Temperaturskalen ist maximal 35 m°K, und die Temperaturabhängigkeit des Unterschiedes ist unregelmässig, wie es *Abb. 3* zeigt.

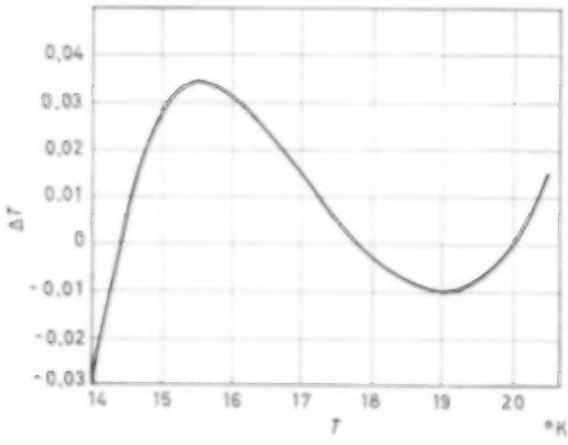

Abb. 3. $\Delta T = T_{\mathrm{WBB}} - T_{\mathrm{L}}$

Neuerdings wurde in Leiden die p–T-Beziehung mit Hilfe von Suszeptibilitätsmessungen an paramagnetischen Salzen neu bestimmt. Es wurde auch durch diese Experimente klar, dass eine sich an die thermodynamische Formel anschliessende Formel die beste ist. Leider sind die zur thermodynamischen Berechnung benutzten Daten nicht so sicher bekannt, wie man das wünschen würde.

Die Suszeptibilitätsmessungen bestimmen die p–T-Beziehung des Wasserstoffs bis auf 0,01°K genau. Wenn man für das He-Temperaturgebiet die

VOL. 2 1961

T_{55}-skala benutzt und 20,38°K für den Siedepunkt des normalen Wasserstoffs annimmt, wird für den Tripelpunkt des normalen Wasserstoffs der Wert 13,94°K gefunden. Der von Woolley, Scott und Brickwedde gemessene Wert ist 13,957. Ein Mittelwert gleich 13,95°K scheint mir heute der empfehlenswerteste zu sein.

(4) Über eine geeignete Weise, Platinwiderstandsthermometer, die an zwei oder drei Fixpunkten geeicht sind, zu interpolieren, möchte ich noch etwas sagen.

Die einfachste Annahme, die man für die Herleitung von Interpolationsformeln machen kann, ist, dass die spezifischen Widerstände der verschiedenen geeichten Thermometer sich nur unterscheiden durch verschiedene temperaturunabhängige Zusatzwiderstände, die von physikalischen und chemischen Defekten herrühren.

Es soll dann die Funktion $(R - R_1)/(R_2 - R_1)$ für alle solche Widerstände gleich sein und man kann sie für die Interpolation benutzen, wenn sie für einen Widerstand mit dem Gasthermometer gemessen ist. Dieses Verfahren genügt nicht für hohe Genauigkeit (bis auf wenige 0,001°K).

Macht man die Annahme, dass der Zusatzwiderstand (r) zwar nicht temperaturunabhängig ist, aber für die verschiedene Widerstände bis auf einen konstanten Faktor (p) und einen konstanten Term (q) die gleiche Temperaturabhängigkeit hat ($R = \zeta + r$ und $r = p\epsilon + q$), dann kann man die folgende Formel benutzen:

$$\frac{R - R_1}{R_2 - R_1} = \frac{\zeta - \zeta_1}{\zeta_2 - \zeta_1} + \frac{p}{R_2 - R_1}\left\{\epsilon - \epsilon_1 - (\epsilon_2 - \epsilon_1)\frac{\zeta - \zeta_1}{\zeta_2 - \zeta_1}\right\}$$

Es sind dann $(\zeta - \zeta_1)/(\zeta_2 - \zeta_1)$ und der Klammerausdruck für alle betrachteten Widerstände gleiche Temperaturfunktionen, und der Unterschied zwischen den $(R - R_1)/(R_2 - R_1)$-Werten von zwei Thermometern ist dem Klammerausdruck proportional. Für diesen Klammerausdruck kann man eine Näherungsformel benutzen, wenn man sie nicht genau kennt oder wenn eine solche einfache Näherungsformel genau genug ist.

Ein Analyse von vorhandenen Ergebnissen zeigt, dass diese Verfahren nur genau genug sind, wenn man sich auf die Platinwiderstandsthermometer von sehr reinem Platin ($\alpha > 0{,}003923$) beschränkt.

Gute Interpolation kann man auch für etwas weniger reines Platin ($\alpha > 0{,}003920$) bekommen, wenn man der Interpolation eine Zweibandvorstellung zugrunde legt. In diesem Fall kann man die folgende Beziehung benutzen:

$$\frac{R}{R_0} = \zeta + \left(w_0 + \frac{p_1\zeta}{\zeta + p_2\eta}\right)\eta$$

mit $\zeta = \zeta/\zeta_0$; $\eta = \epsilon - \epsilon_0\zeta$; $w_0 = R_{00}/R_0$; R_0 Eispunktwiderstand; R_{00} Widerstand für $T = 0$; p_1 und p_2 Konstanten.

VOL.
2
1961

THERMODYNAMISCHE TEMPERATURSKALA, IHRE REALISIERUNG ZWISCHEN 90° UND 1500°K

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Seit Lord Kelvin im Jahre 1852 gezeigt hat, daß sich auf den zweiten Hauptsatz der Thermodynamik eine Temperaturskala gründen läßt, die unabhängig von speziellen Stoffeigenschaften ist, war es nicht mehr zweifelhaft, daß dieser thermodynamischen Skala die Zukunft gehören würde. Sie ist denn auch bis auf den heutigen Tag die Grundlage aller Temperaturmessungen geblieben, und es sind besonders um die Jahrhundertwende große Anstrengungen gemacht worden, die praktischen Methoden der Temperaturmessung an die thermodynamische Skala anzuschließen.

Um thermodynamische Temperaturen zahlenmäßig angeben zu können, genügt der zweite Hauptsatz allein nicht. Dazu ist noch die Festlegung der Temperatureinheit, die sich nicht ohne Zwang in das C.G.S-System einordnen läßt, *per definitionem* erforderlich. Dies ist bis vor einigen Jahren nach dem Vorschlag von Celsius (1742) dadurch geschehen, daß man das Temperaturintervall zwischen dem normalen Eisschmelzpunkt und dem normalen Wassersiedepunkt in 100 Grade eingeteilt hat, obwohl bereits Lambert (1760), Lord Kelvin u.a. darauf hingewiesen haben, daß für die Festlegung der Temperatureinheit ein einziger Fixpunkt genügt, wenn diesem ein bestimmter Temperaturwert zugeordnet wird. Dieser Gedanke ist im Jahre 1954 dadurch verwirklicht worden, daß die 10. Generalkonferenz für Maß und Gewicht[1] in Paris beschlossen hat, die thermodynamische Temperaturskala auf einen einzigen Fixpunkt, nämlich den mit sehr großer Genauigkeit reproduzierbaren Wassertripelpunkt, zu gründen und diesem den Temperaturwert 273,16°K zuzuteilen. Der Wassertripelpunkt dient seitdem als Bezugstemperatur für alle thermodynamischen Temperaturmessungen. Er liegt um 0,01 grd höher als der normale Eisschmelzpunkt, von dem aus, wie bisher, die Celsiustemperaturen gemessen werden.

Diese Neudefinition der Temperatureinheit ist z.Z. mehr von prinzipieller als von praktischer Bedeutung, denn der Wert 273,16°K ist so gewählt, daß die Temperaturdifferenz zwischen dem normalen Eisschmelzpunkt und Wassersiedepunkt innerhalb der Unsicherheit der heutigen thermodynamischen Meßverfahren 100,00 grd bleibt. Es ist jedoch möglich, daß mit Verfeinerung dieser Verfahren Abweichungen von dieser Differenz bis zu $\pm$ 0,005 grd gefunden werden, da der normale Wassersiedepunkt nach der Neudefinition kein Fundamentalpunkt mehr ist.

1. FUNDAMENTALE MEßVERFAHREN

Der zweite Hauptsatz der Thermodynamik liefert viele Gesetzmäßigkeiten, auf die sich eine thermodynamische Temperaturmessung stützen

könnte (z.B. Carnotscher Kreisprozeß, Joule–Thomson-Effekt, Clausius–Clapeyronsche Gleichung). Es ist bemerkenswert, daß oberhalb von 90°K bisher von diesen Möglichkeiten der Temperaturmessung kaum Gebrauch gemacht wurde, einerseits weil die darauf zu gründenden Meßverfahren in der Durchführung zu schwierig und umständlich sind, andererseits weil die zu erwartende Meßgenauigkeit nur gering ist. Die wenigen Methoden, die praktisch für die direkte Messung thermodynamischer Temperaturen in Frage kommen, stützen sich fast ausschließlich auf Beziehungen, die nicht aus dem zweiten Hauptsatz ableitbar, sondern entweder auf statistischem Wege theoretisch begründet sind oder auf einem Erfahrungssatz beruhen. Trotzdem ist es nicht zweifelhaft, daß die mit ihnen gemessenen Temperaturen mit den thermodynamischen identisch sind.

Gasthermometer

Das gasthermometrische Verfahren ist im Temperaturbereich von 90°K bis 1500°K das genaueste und bei weitem am häufigsten angewendete. Es stützt sich auf die zunächst empirisch gefundene und später mit Hilfe der kinetischen Gastheorie begründete Tatsache, daß das Produkt aus dem Druck p und dem Volumen v eines Gases bei hinreichender Verdünnung (idealer Gaszustand) für alle Gase eine eindeutige Funktion der Temperatur T ist:

$$pv = CT \tag{1}$$

Unter dieser Voraussetzung läßt sich über einen Carnotschen Kreisprozeß beweisen, daß die so gefundene Temperatur mit der thermodynamischen identisch ist.

Da sich, wie oben bemerkt, die Temperatureinheit nicht ohne Zwang auf andere Einheiten des C.G.S.-Systems zurückführen läßt, kann eine thermodynamische Temperatur mit Hilfe der Zustandsgleichung (1) nur relativ zu einer Bezugstemperatur T_b bestimmt werden. Jede gasthermometrische Messung geschieht daher in der Weise, daß die Zustandsgrößen p, v und T in zwei verschiedenen thermodynamischen Zuständen gemessen werden und das Verhältnis T/T_b gebildet wird, wobei die Konstante C (Gl.(1)) herausfällt. Als Bezugstemperatur T_b wird zweckmäßigerweise die Temperatur des Wassertripelpunktes gewählt, deren Wert (273,16°K) durch Definition festliegt (s.o.). Je nachdem, ob bei der Zustandsänderung das Volumen v oder der Druck p konstant gehalten wird, unterscheidet man die *speziellen Methoden konstanten Volumens oder konstanten Druckes*. In beiden Fällen muß das Gasthermometergefäß von T_b auf T erwärmt oder abgekühlt werden, wobei im allgemeinen störende Sorptionseffekte auftreten. Diese können mit der neueren *speziellen Methode "konstanter Gefäßtemperatur"* weitgehend vermieden werden. Das Gasthermometergefäß befindet sich bei diesem Verfahren dauernd auf der zu messenden Temperatur T und ist über eine Kapillare mit einem auf der Bezugstemperatur T_b gehaltenen und zunächst mit Quecksilber gefüllten Zusatzgefäß verbunden. Die Zustandsänderung wird durch Freigabe des ausgemessenen Zusatzvolumens bewirkt, wobei ein Teil des Gases im Thermometergefäß in das Zusatzgefäß strömt und dessen Temperatur annimmt.

Die Reduktion der mit realen Gasen durchgeführten Messungen auf den idealen Gaszustand bereitet im allgemeinen keine Schwierigkeiten. Sie

geschieht entweder mit Hilfe von Korrektionen, die aus den 2. Virialkoeffizienten der Gase bestimmt werden*, oder durch Extrapolation der bei verschiedenen Anfangsdrucken gasthermometrisch gemessenen Temperaturen auf den Druck Null. Es hat sich gezeigt, daß auf diese Weise selbst bei 1000°C innerhalb der Meßunsicherheit von ± 0,1°C mit verschiedenen Gasen gleiche Temperaturwerte erhalten werden, wodurch die Unabhängigkeit der Ergebnisse von speziellen Stoffeigenschaften genügend gesichert ist.

Bezüglich Einzelheiten der bei hohen Genauigkeitsansprüchen komplizierten und besonders in höheren Temperaturen schwierig durchzuführenden gasthermometrischen Messungen muß auf die Originalliteratur verwiesen werden[3]. Es möge hier nur erwähnt werden, daß sich nach Ansicht des Verfassers bei dem heutigen Stand der Meßtechnik zwischen − 180° und + 200 °C eine Genauigkeit von mindestens ± 0,01 grd, bei 500°C von etwa ± 0,02 grd und bei 1000°C von etwa ± 0,1 grd bei sorgfältiger Ausschaltung systematischer Fehler erreichen läßt. Das dürften die höchsten Genauigkeiten sein, mit denen thermodynamische Temperaturen im Bereich von − 180° bis 1200°C derzeit gemessen werden können. Leider hat die Angleichung der praktischen Internationalen Temperaturskala an die thermodynamische Skala bis zu diesem Genauigkeitsgrad noch nicht erfolgen können, so daß bei praktischen Temperaturmessungen besonders in höheren Temperaturen mit erheblich größeren Unsicherheiten gerechnet werden muß (vgl. *Abb.* 1). Der Grund liegt darin, daß die heutige Angleichung im wesentlichen noch auf gasthermometrischen Messungen beruht, die vor 1914 durchgeführt worden sind und den heute möglichen Genauigkeitsgrad nicht erreicht haben. Spätere vereinzelte Messungen verschiedener Autoren lassen zwar die Richtung erkennen, in der eine Änderung der Internationalen Temperaturskala vorgenommen werden müßte; sie sind jedoch zu wenig zahlreich und noch nicht genügend in Übereinstimmung, um jetzt schon eine entsprechende internationale Vereinbarung zu ermöglichen. Es ist zu hoffen, daß sich dieser Zustand in den nächsten Jahren ändern wird.

Optisch pyrometrische Verfahren mit schwarzem Strahler

Die Strahldichte eines schwarzen Strahlers—im allgemeinen realisiert durch einen Hohlraumkörper mit kleiner Öffnung—ist unabhängig von speziellen Stoffeigenschaften und eine eindeutige Funktion der thermodynamischen Temperatur. Je nachdem, ob die Gesamt- oder die Teilstrahldichte gemessen wird, unterscheidet man:

(a) *Teilstrahlungspyrometer*

Die Meßgrundlage liefert die Plancksche Strahlungsformel

$$V_T = \frac{\exp c_2/\lambda T_b - 1}{\exp c_2/\lambda T - 1} \qquad (2)$$

* Erforderlich ist die Kenntnis der zweiten Virialkoeffizienten K_b und K_T bei der Bezugstemperatur T_b und der zu messenden Temperatur T, wobei K_b experimentell im allgemeinen mit ausreichender Genauigkeit ermittelt werden kann. K_T braucht umso weniger genau bekannt zu sein je höher T ist. So entspricht z.B. einer Unsicherheit des K_T von 10 Prozent am Goldpunkt nur ein Fehler der thermodynamischen Temperatur dieses Punktes von 0,04° bis 0,06°C.

Man bestimmt das Verhältnis V_T der Teilstrahldichten eines schwarzen Strahlers bei den Temperaturen T und T_b und bei gleicher Wellenlänge λ. Die Konstante c_2 kann aus atomaren und allgemeinen Konstanten der Physik berechnet werden. Dieses Verfahren bildet einen Teil der Internationalen Temperaturskala (vgl. **2**).

(b) *Gesamtstrahlungspyrometer*

Durch Integration der Planckschen Strahlungsformel über alle Wellenlängen erhält man das Stephan–Boltzmannsche Gesetz, das sich auch aus dem zweiten Hauptsatz der Thermodynamik ableiten läßt. Aus diesem Gesetz folgt für das Verhältnis V_G der Gesamtstrahldichten eines schwarzen Strahlers bei den Temperaturen T und T_b die Beziehung:

$$V_G = \frac{T^4}{T_b^4} \tag{3}$$

Vorteilhaft ist bei diesem Verfahren die große Strahlintensität und die Unabhängigkeit von einer Strahlungskonstanten; indessen ist es bei genauen Messungen schwierig, die Strahlung über alle Wellenlängen vollständig zu erfassen und Absorptionseffekte genügend auszuschalten.

Die optisch pyrometrischen Verfahren dienen hauptsächlich oberhalb des Golderstarrungspunktes (internationaler Wert 1336,15°K = 1063°C) zur Realisierung der thermodynamischen Temperaturskala. Die Verfeinerung dieser Meßverfahren, insbesondere durch Entwicklung objektiver Pyrometer, hat dazu geführt, daß mit ihnen heute oberhalb des Goldpunktes eine größere Genauigkeit erreicht werden kann, als es mit Hilfe von Gasthermometern möglich erscheint. Es muß jedoch darauf hingewiesen werden, daß sich jede optische Temperaturmessung auf eine gasthermometrische gründen muß, da es praktisch nicht möglich ist, den Wassertripelpunkt wegen zu geringer Strahlintensität als Bezugstemperatur der optischen Skala zu wählen. Diese stützt sich vielmehr auf den Goldpunkt, der kein Fundamentalpunkt der thermodynamischen Skala ist und dessen gasthermometrischer Bestimmung daher erhöhte Bedeutung zukommt.

"Rausch"-Thermometer

Auf den Zusammenhang, der zwischen den durch die Wärmebewegung bedingten statistischen Schwankungen und der thermodynamischen Temperatur besteht, läßt sich ein weiteres fundamentales Meßverfahren gründen. Aus der statistischen Thermodynamik folgt, daß die mittlere quadratische Spannungsschwankung $\overline{V}^2$ zwischen den Enden eines elektrischen Widerstandes R im Frequenzbereich Δf der thermodynamischen Temperatur T sowie Δf und R proportional ist (Nyquist). Bringt man daher einen Widerstand R auf die Temperatur T und reguliert man einen auf der Bezugstemperatur T_b befindlichen Widerstand R_b so lange, bis an beiden Widerständen im gleichen Frequenzbereich dieselbe quadratische Rauschspannung $\overline{V}^2$ herrscht, so gilt:

$$\frac{T}{T_b} = \frac{R_b}{R} \tag{4}$$

Garrison und Lawson[3] haben im Jahre 1949 eine auf dieser Grundlage beruhende Temperaturmeßeinrichtung beschrieben und bei 1000°C eine

Genauigkeit von 1 bis 2 grd erreicht. Ob sich diese steigern läßt, kann heute noch nicht übersehen werden; immerhin ist ein prinzipiell neuer Weg der Realisierung der thermodynamischen Temperaturskala aufgezeigt worden.

2. PRAKTISCHE MEßVERFAHREN (INTERNATIONALE TEMPERATURSKALA)

Die unter **1** beschriebenen fundamentalen Meßverfahren zur Realisierung der thermodynamischen Temperaturskala sind im allgemeinen schwierig und z.T. nur mit großem experimentallem Aufwand durchführbar. Sie werden daher praktisch selten angewendet. Wesentlich leichter realisierbar ist die Internationale Temperaturskala, die erstmalig im Jahre 1927 von der 7. Generalkonferenz für Maß und Gewicht festgelegt und im Jahre 1948 von der 9. Generalkonferenz in einigen Punkten abgeändert wurde[4].

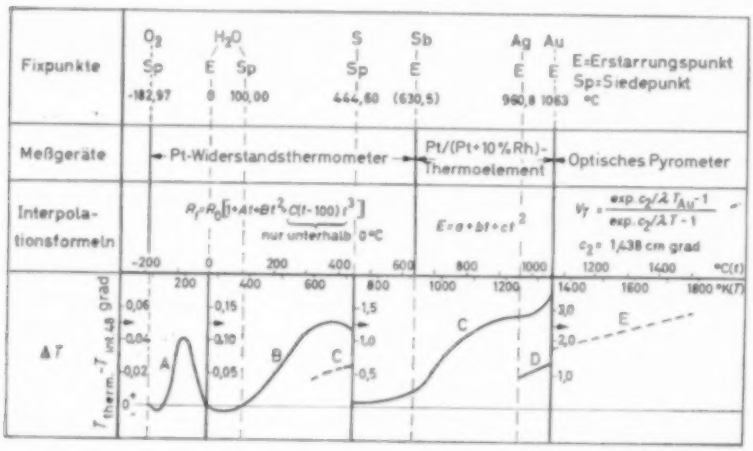

Abb. 1. Internationale Temperaturskala 1948: A, Mittel aus Leidener und P.T.R.-Messungen[5]; B, nach M.I.T.-Mussengen[6]; C, nach P.T.B.-Messungen[7]; D, nach Messungen im Tokyo Institute of Technology[8]; E, extrapoliert mit $T_{Au} = 1064{,}76°$ statt 1063°C, $c_2 = 1{,}4388^{(9)}$ statt 1,438 cm grd

Die Internationale Temperaturskala 1948 bildet heute die Grundlage aller praktischen Temperaturmessungen. Sie wird verwirklicht einerseits durch eine Anzahl gut reproduzierbarer Fixpunkte, denen bestimmte Temperaturwerte zuerteilt sind, andererseits durch Interpolationsinstrumente, die an diese Fixpunkte nach bestimmten Vorschriften angeschlossen werden. Ihre Reproduzierbarkeit ist wesentlich größer als die der thermodynamischen Skala. An diese ist die internationale Skala dadurch angeglichen, daß ihren Fixpunkten gasthermometrisch gemessene Werte zugrunde gelegt werden, die jedoch im wesentlichen noch aus den Jahren vor 1914 stammen. Einzelheiten sind aus *Abb. 1* zu ersehen.

In *Abb. 1* sind insbesondere auch die Abweichungen ΔT zwischen der Internationalen Temperaturskala 1948 und der thermodynamischen Skala eingetragen, mit denen man auf Grund neuerer gasthermometrischer

Messungen rechnen muß und die z.T. nicht unerheblich sind*. Im allgemeinen liefert die Internationale Temperaturskala etwas zu tiefe thermodynamische Temperaturen. Hinsichtlich der Größe der Abweichungen beider Skalen bestehen leider zwischen verschiedenen Beobachtern noch gewisse Differenzen, die erst aufgeklärt werden müssen, bevor eine bessere Angleichung der internationalen Skala an die thermodynamische erfolgen kann. Solange dies nicht geschehen ist, wird man bei der Bestimmung thermodynamischer Temperaturen mit Hilfe eines praktischen Meßverfahrens der Internationalen Temperaturskala mit Unsicherheiten zu rechnen haben, die den in *Abb. 1* dargestellten maximalen Abweichungen entsprechen. Benutzt man ein anderes, nichtthermodynamisches Meßverfahren oder Gerät (z.B. Quecksilberthermometer), so kommen natürlich die Fehler bei dessen Anschluß an die internationale Skala noch hinzu.

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* Die in *Abb. 1* dargestellten ΔT-Werte zwischen Schwefel- und Goldpunkt bedürfen auf Grund der neuesten Messungen über die Ausdehnung des Quarzglases (Gasthermometergefäß), die in die Temperaturmessung eingeht, einer Korrektur. Sie müssen beim Goldpunkt um etwa 0,3°C, beim Silberpunkt um etwa 0,2°C und beim Antimonpunkt um etwa 0,05°C erniedrigt werden, während sie beim Schwefelpunkt unverändert bleiben.

THERMODYNAMISCHE TEMPERATURSKALA, IHRE REALISIERUNG AN FESTEN KÖRPERN FÜR TEMPERATUREN OBERHALB 1500°K

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Die praktische Realisierung der thermodynamischen Temperaturskala durch das Gasthermometer reicht gegenwärtig bis zur Temperatur des Goldschmelzpunktes. Die Ausdehnung dieser Skala nach höheren Temperaturen ist mit Hilfe der Strahlungsgesetze des schwarzen Körpers möglich, da diese im Einklang mit dem zweiten Hauptsatz stehen und die hier auftretenden Temperaturen thermodynamische Temperaturen sind. Bekanntlich wird das Stephan–Boltzmannsche Gesetz der Gesamtstrahlung auch als direkte Folge des zweiten Hauptsatzes abgeleitet.

Die Internationale Temperaturskala[1], welche die thermodynamische möglichst genau wiedergeben soll, benutzt daher auch die Strahlungsgesetze, um die Temperaturskala nach oben auszudehnen. Sie setzt ein Verfahren fest, nach dem die Extrapolation vorgenommen werden soll. Hiernach wird die Temperatur T eines schwarzen Körpers oberhalb des Goldschmelzpunktes (T_{Au}) gemessen, indem für eine im Sichtbaren gelegene Wellenlänge λ das Verhältnis V der Strahldichten dieses schwarzen Körpers und des auf den Goldschmelzpunkt gehaltenen bestimmt wird. T wird also erhalten aus

$$V = \frac{\exp \frac{c_2}{\lambda T_{Au}} - 1}{\exp \frac{c_2}{\lambda T} - 1}$$

Hier treten zwei Konstanten auf, c_2 und T_{Au}, deren Zahlenwerte in der Internationalen Temperaturskala festgesetzt werden.

Das Strahldichteverhältnis läßt sich in der Weise bestimmen, daß durch eine genau ausgemessene Lichtschwächung—z.B. ein rotierender Sektor bekannter Öffnung—die Strahldichte des höher temperierten schwarzen Körpers auf die des auf den Goldschmelzpunkt gehaltenen erniedrigt wird. Für diese Messung und für die Ermittlung der Temperaturen auf Grund der Strahlungsgesetze verwendet man die bekannten optischen Pyrometer. Die Internationale Temperaturskala 1948 hat die Konstanten in der obigen Beziehung zu $T_{Au} = (1063 + 273{,}15)$°K und $c_2 = 1{,}438$ cm °K festgesetzt. Beide Werte scheinen nach unserer gegenwärtigen Kenntnis zu niedrig zu sein. Neue Präzisionsmessungen[2] haben für den Goldschmelzpunkt 1337,6°K geliefert. Der Zahlenwert für c_2 kann aus den gut bekannten Atomkonstanten zu $c_2 = 1{,}4388$ cm°K berechnet werden, nähert sich also dem Wert 1,439. Wenn künftige Untersuchungen diese Zahlenwerte bestätigen, wird die Generalkonferenz für Maß und Gewicht die Konstanten neu festsetzen müssen.

Diese Betrachtungen bezogen sich nur auf den schwarzen Körper. Will man die Temperatur eines beliebigen Strahlers messen, so kann man diese Aufgabe auf die Temperaturmessung eines schwarzen Körpers zurückführen, der sich mit dem zu untersuchenden Strahler im Wärmegleichgewicht befindet.

Über Methoden zur Ermittlung der Temperaturen fester Körper soll hier kurz berichtet werden. Die Beschränkung auf nur diese Körper setzt eine obere Temperaturgrenze fest, die bei rd. 4300°K liegt.

Die Forderung, daß der zu untersuchende Körper im Wärmegleichgewicht mit einem schwarzen Körper stehen muß, kann man in vielen Fällen durch geeignete Formgebung des Kärpers erfüllen, z.B. bei Metallen, indem man sie als Zylinder von geringer Wandstärke auslegt und mit einer kleinen Öffnung für den Durchtritt der schwarzen Strahlung versieht. Temperaturmessungen mit solchen Anordnungen sind in der Literatur vielfach beschrieben worden. Die Schmelzpunkte der Edelmetalle hat man mit großer Genauigkeit ermittelt, indem man einen Hohlkörper aus einem Material, das nicht mit dem Metall reagierte, in diese tauchte und die aus einer Öffnung des Hohlkörpers austretende schwarze Strahlung während des Haltepunktes beim Schmelzen oder Erstarren für die Temperaturmessung ausnutzte.

Eine weitere Möglichkeit, die Temperatur eines beliebigen Temperaturstrahlers zu ermitteln, liefert das Kirchhoffsche Gesetz. Der Betrag der in einem abgegrenzten Spektralbereich ausgestrahlten Leistung des Strahlers, dividiert durch den Wert seines Absorptionsgrades, ist hiernach ebenso groß wie die Strahlungsleistung des schwarzen Körpers gleicher Temperatur in dem gleichen Spektralbereich. Dieses allgemein gültige Gesetz steht ebenfalls im Einklang mit dem zweiten Hauptsatz, da man bei Nichterfüllung Widersprüche gegen ihn ableiten könnte. Hiernach kann man die wahre Temperatur eines beliebigen Temperaturstrahlers messen, wenn man seinen Absorptionsgrad kennt. Im allgemeinen muß dieser Wert durch eine zusätzliche Messung bestimmt werden.

Es sind auch Versuchsanordnungen entwickelt worden, die eine Messung des Absorptionsgrades umgehen. Sie beruhen darauf, durch eine zusätzliche Bestrahlung des zu untersuchenden Körpers zu erreichen, daß die von ihm in eine bestimmte Richtung reflektierte Strahlung, vermehrt um die auf Grund seiner thermischen Energie in diese Richtung emittierte Strahlung, ebenso groß ist wie die eines schwarzen Körpers gleicher Temperatur. Läßt man beispielsweise Strahlung eines schwarzen Körpers auf einen erhitzten Körper fallen, dessen Oberfläche regulär reflektiert, und vergleicht man die Strahldichte der von seiner Oberfläche ausgesandten, aus reflektiertem Anteil und Eigenemission bestehenden Strahlung mit der Strahldichte des schwarzen Körpers, so stimmen beide nur dann überein, wenn der Körper und der schwarze Strahler gleiche Temperatur haben. Ein Gerät, das nach diesem Verfahren arbeitet, hat Fastie[3] angegeben.

Dasselbe Resultat kann man auch erzielen, wenn man den erhitzten Körper in der Mitte einer Ulbrichtschen Kugel[4] anordnet, deren Innenwand überall gleichmäßig beleuchtet wird (*Abb. 1*). Durch eine Öffnung in der Kugelwand betrachtet, leuchtet die Wand in der Beobachtungsfarbe

VOL. 2 1961

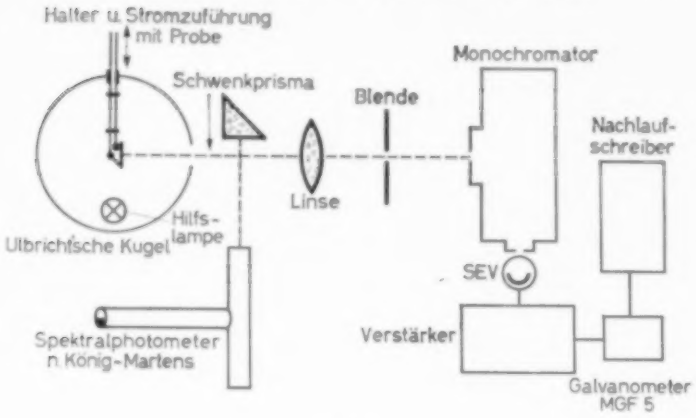

Abb. 1

mit einer Helligkeit, der man eine scheinbare Temperatur zuordnen kann, nämlich die Temperatur eines schwarzen Körpers, der in der Beobachtungsfarbe die gleiche Helligkeit aufweist. Der erhitzte Körper in der Kugelmitte strahlt durch die Öffnung der Kugelwand außer seiner Eigenstrahlung auch Wandstrahlung, die an dem Körper reflektiert worden ist. Kann man die Helligkeit der Kugelwand so regeln, daß der Körper in der Kugelmitte im Gesichtsfeld verschwindet, dann ist die der Helligkeit der Kugelwand zugeordnete Temperatur gleich der thermodynamischen Temperatur des Körpers in der Kugelmitte. Bei diesem Verfahren ist es gleichgültig, ob die Oberfläche des Körpers die Wandstrahlung regulär nach dem Reflexionsgesetz oder diffus zurückstrahlt. Leider reichen die Temperaturen, die man nach dieser Methode ermitteln kann, nur bis etwa 1700 K.

In der gleichen Anordnung kann man auch den Absorptionsgrad beliebiger Körper bestimmen. Man wird unabhängig von der Temperatur des Körpers, wenn man die Kugelwand durch Wechsellicht gleichmäßig ausleuchtet. Der Körper in der Kugelmitte wird durch die Öffnung in der Wand auf eine Photozelle abgebildet, die an einen auf die Wechsellichtfrequenz abgestimmten Verstärker angeschlossen ist. Zur Anzeige gelangt dann nur das an dem Körper reflektierte und, nach Fortnahme dieses Körpers aus dem Strahlengang, das einfallende Wechsellicht.

Ein anderes Verfahren[8], das ebenfalls ohne Kenntnis des Absorptionsgrades die wahre Temperatur eines glühenden Körpers zu messen gestattet, stützt sich auf die Eigenschaft des schwarzen Körpers, nur unpolarisierte Strahlung auszusenden. Im Gegensatz dazu ist die von einem glühenden Metall seitlich emittierte Strahlung weitgehend polarisiert. Fällt unpolarisiertes Licht unter einem Winkel α (z.B. $\alpha = 45°$) auf eine glühende Metallfläche, so wird die aus reflektiertem Anteil und thermischer Emission zusammengesetzte Strahlung in der Reflexionsrichtung im allgemeinen noch polarisierte Komponenten enthalten. Bei einer bestimmten Strahldichte der auftreffenden Strahlung kann jedoch erreicht werden, daß die

zusammengesetzte Strahlung unpolarisiert ist. Sie stimmt dann überein mit der Strahlung eines schwarzen Körpers, der die gleiche Temperatur wie das Metall hat.

Die Richtigkeit dieser Behauptung folgt aus dem Kirchhoffschen Gesetz, wenn man dieses auf die polarisierten Anteile der von der untersuchten Oberfläche unter dem Winkel α ausgehenden Strahlung anwendet. Die Strahldichten, denen in der Emissionsebene bzw. senkrecht dazu schwingende elektrische Feldstärken zugeordnet sind, verden bestimmt durch $J_{\lambda T}(1 - R_{\parallel})$ bzw. $J_{\lambda T}(1 - R_{\perp})$.

Hierin ist $J_{\lambda T}$ die Strahldichte einer geradlinig polarisierten Komponente der schwarzen Strahlung von der Temperatur T und $R_{\parallel}, R_{\perp}$ bedeuten die Reflexionsgrade der Metalloberfläche für polarisiertes Licht der betrachteten Art. Die zusammengesetzte Strahlung hat in den beiden Schwingungsrichtungen des elektrischen Vektors die Strahldichten $J_{\lambda T}(1 - R_{\parallel}) + KR_{\parallel}$ bzw. $J_{\lambda T}(1 - R_{\perp}) + KR_{\perp}$. $2K$ ist die Strahldichte der auftreffenden unpolarisierten Strahlung. Wenn die zusammengesetzte Strahlung unpolarisiert ist, was durch ein in den Strahlengang gestelltes Polarisationsfilter erkannt werden kann, gilt

$$J_{\lambda T}(1 - R_{\parallel}) + KR_{\parallel} = J_{\lambda T}(1 - R_T) + KR_{\perp} \text{ oder}$$
$$(J_{\lambda T} - K)(R_{\perp} - R_{\parallel}) = 0$$

Da nach den Fresnelschen Formeln stets $R_{\perp} > R_{\parallel}$ ist, folgt $K = J_{\lambda T}$. Damit wird die Strahldichte jeder geradlinig polarisierten Komponente der zusammengesetzten Strehlung gleich $J_{\lambda T}$, also gleich der des schwarzen Körpers von der gesuchten Temperatur T.

Eine Anordnung zur Ermittlung der wahren Temperatur glühender Metalle nach diesem Prinzip ist in *Abb. 2* wiedergegeben. Es handelt sich speziell um die Temperaturermittlung an einem Wolframband. Lampe A ist eine Bandlampe mit einem 2 mm breiten, horizontal ausgelegten Wolframband, dessen wahre Temperatur an einer definierten Stelle in der Bandmitte

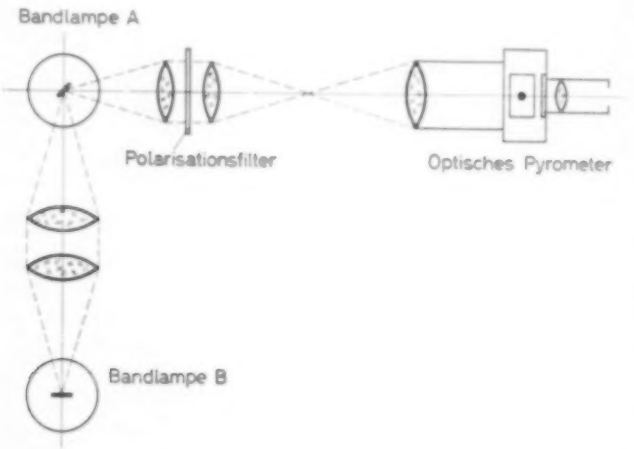

Abb. 2

VOL. 2 1961

gemessen werden soll. Die unpolarisierte Strahlung, die an dem Band reflektiert wird, entstammt einer zweiten Bandlampe B mit vertikal ausgerichtetem Band, aus dem nur die senkrecht austretende, also unpolarisierte Strahlung für die Beobachtungen ausgenutzt wird. Das Band der Lampe B wird auf die Beobachtungsstelle der Lampe A abgebildet. In der Reflexionsrichtung befindet sich ein optisches Pyrometer, mit dem die Beobachtungsstelle anvisiert wird. Im Strahlengang vor dem Pyrometer ist eine Polarisationsfolie angeordnet. Die Ausstrahlung der Lampe B muß nun so geregelt werden, daß sich bei einer Drehung der Polarisationsfolie die pyrometrische Einstellung nicht ändert. Ist dieser Zustand erreicht, dann liefert die pyrometrische Abgleichung nach Fortnahme des Filters und unter Berücksichtigung der Lichtschwächung durch die Glasmedien zwischen leuchtendem Band und Pyrometer direkt die wahre Temperatur des Bandes. Jedoch ist jetzt noch eine Einschränkung zu machen. Da nämlich Lampe A auch zur Lampe B polarisiertes Licht sendet, das, dort reflektiert, wieder nach A gelangt, ist die Voraussetzung verletzt, daß nur unpolarisierte Strahlung auf A trifft. Daher liefert das Verfahren einen Temperaturwert, der von der wahren Bandtemperatur um einen geringen Betrag abweicht. Der Unterschied kann jedoch in der gleichen Anordnung bestimmt oder so klein gehalten werden, daß er vernachlässigbar ist. Natürlich entfallen alle Korrektionen, wenn Lampe B durch einen schwarzen Körper ersetzt wird.

Außer den hier besprochenen Verfahren, die sich auf allgemein gültige thermodynamische Naturgesetze stützen, sind andere Methoden entwickelt worden, denen dieses Fundament fehlt. Sie verfolgen das Ziel, die sogenannte Verteilungstemperatur zu messen, die in vielen Fällen der wahren Temperatur nahe liegt. Hierauf soll jedoch nicht eingegangen werden.

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VOL.
2
1961

DESIGN AND USE OF ANEROID BOMB CALORIMETERS

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(1) The object of a bomb calorimeter is to absorb the heat released from an accurately measured amount of chemical reaction and convert it into a temperature rise which can be measured with corresponding accuracy. Questions associated with the chemical reaction are often difficult, but will not be discussed here. This paper is concerned with the purely physical questions associated with the temperature rise. It is also concerned, in part, with the physical problem of producing a comparable temperature rise by introducing accurately measured Joule heat within the calorimeter. This procedure is necessary when the calorimeter is used for evaluating a thermochemical standard material, such as benzoic acid, with the intention of using it to measure the equivalents of other bomb calorimeters in which heat will be generated by combustion only.

Reasons will be put forward for believing that aneroid bomb calorimeters are capable of higher accuracy than conventional calorimeters in which the heat is absorbed in well stirred water. It will be contended that aneroid calorimeters can be designed which are simpler, and quicker in use, than stirred-water calorimeters.

(2) Apart from chemical considerations, the first requirement of a calorimeter is that its equivalent should be repeatable every time it is assembled, except for small variations in mass of substance, platinum, fuse and auxiliary material for which corrections can be made. The presence in the conventional calorimeter of water, whose heat of evaporation is very high, means that great care must be taken in design and assembly to minimize the evaporation and condensation of water, and to reproduce in every experiment any movements of water which are unavoidable.

(3) The rate of transfer of heat $\dot{Q}$ between the calorimeter and its surroundings, during the period of the experiment, must obey an unchanging law such as $\dot{Q} = k(T - T_e)$ where T is the temperature of the thermometer in the calorimeter, and k and T_e remain constant throughout the experiment. Corrections can be applied, for example, if T in the equation differs for part of the time from the temperature of the thermometer; but errors are unavoidable if k and T_e do not remain constant.

It is clearly an advantage if k is small, and this is best achieved by evacuating the space between the calorimeter and its outer jacket, and by lengthening the electrical leads which cross this space. Vacuum spaces are not usually possible round stirred-water calorimeters.

As to the problem of keeping k constant, investigations by White[1] and others have shown that k is affected mainly by water vapour movement and by convection of air in the space surrounding the calorimeter. The

width of this space must be limited to 1 cm if it is not evacuated, and convection is still not fully eliminated, with the consequence that the temperature of the calorimeter must be kept within 1 to 1·5°C of its outer jacket. Convection in the air turns out to be the factor which restricts the permissible temperature rise in stirred-water bomb calorimetry to about 2°C.

(4) A calorimeter must reach a uniform temperature within 5 to 10 minutes after heat is generated within it. If a steel bomb is used, the only way to achieve such quick equilibrium is by surrounding it with well stirred water. There is only one metal, namely silver, whose thermal diffusivity is high enough for equally quick equilibrium to be reached without using stirred water, as *Table 1* shows. The values for the duration of the middle

Table 1. Duration of middle period in bomb calorimeter

Type	*Mass of benzoic acid* (g)	*Diffusivity* (cm^2/sec)	*Middle period*	
			Combustion (min)	*Electrical* (min)
Steel bomb in stirred water	1·3	—	10	11·5
Silver (Ag 92·5, Cu 7·5) bomb	0·2	1·6	5	8·5
Silver bomb (estimated)	1·3	1·6	10	13·5
Copper bomb (0·05% Te)	1·0	1·1	14	—
Brass bomb } estimated from surface tem-	1·3	0·34	90	—
Steel bomb } perature changes	1·3	0·12	300	—

period, during which equilibrium is being reached in the calorimeter, are approximately proportional to the inverse of its thermal diffusivity.

(5) *Figure 1* shows the construction of a small silver bomb calorimeter made at the National Physical Laboratory. The oxygen space is 97 ml, and 0·2 g of benzoic acid burns completely in oxygen at a pressure of 25 atm, producing a temperature rise of 3·5°C. A 1 in 5 scale model withstood an internal pressure of 500 atm without permanent deformation. The mass of silver is about 5·5 kg, and its equivalent is 1350 J/°C. A manganin heater of 10Ω is fixed inside the bomb to allow electrical determination of the equivalent.

The heat transfer coefficient, k, is 1·2 J $°C^{-1}$ min^{-1}. This is about 0·025 of the k of stirred-water calorimeters, but these have about seven times the equivalent of the silver bomb and are used with a rather smaller temperature rise. The standard deviation of individual estimates of the equivalent, the bomb being dismantled and reassembled each time, was less than 1 part in 7000. The standard deviation of individual estimates of the heat of combustion of benzoic acid, involving one combustion and one electrical experiment, was less than 1 part in 5000.

An interesting technical innovation is the method of filling the bomb with oxygen through a stainless steel hypodermic tube, pushed through the neoprene O-ring which seals the bomb. The O-ring reseals after the hypodermic tube is withdrawn. A full account of this bomb calorimeter will be shortly submitted for publication[4].

(6) Under the rigorous conditions needed for the determination of the heat of combustion of thermochemical standard benzoic acid, it was found

VOL. 2 1961

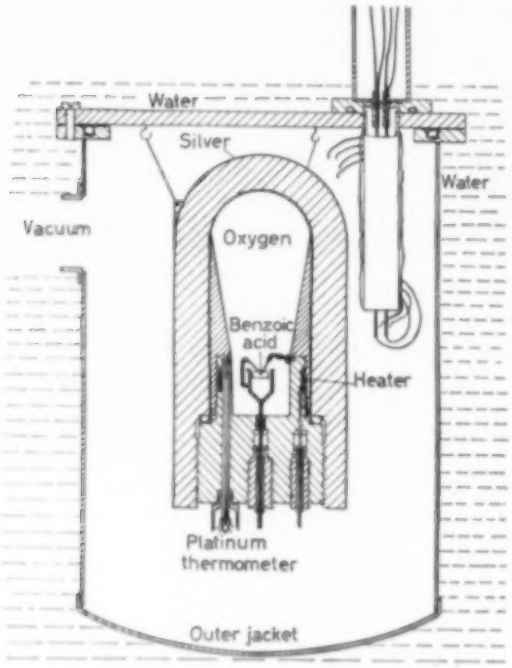

Figure 1. Aneroid bomb calorimeter

that the silver bomb produced results at least twice as quickly as a conventional stirred-water calorimeter. For routine determinations of the heats of formation of organic compounds, the silver bomb should again save time. For determinations of less than 0·1 per cent accuracy, the saving of time may be less noticeable, because about 30 min is needed for pumping the vacuum space and 30 min for filling with oxygen.

The chemical reactions associated with the combustion of sulphur compounds and other materials require a bomb to be rotated and turned over. The necessary mechanical power can, without too much difficulty, be transmitted into the vacuum space of an aneroid bomb calorimeter, or it can be generated there. Since the vacuum space can be quite large, the mechanical problems should indeed be easier in the vacuum round an aneroid bomb than in the water round a steel bomb.

Because of the difficulty of making stirred-water calorimeters of low heat capacity, it is possible that there may be special uses for small silver bomb calorimeters such as the one described. On the other hand there is no reason, except the cost of the silver, to prevent the construction of much larger silver bombs.

(7) The heat of combustion of benzoic acid under standard bomb conditions has just been estimated by the N.P.L. silver aneroid bomb calorimeter to be 26431·7 J/g, with a standard error of 2·2 J/g. This may be compared with the eleven most recently published estimates of the same

constant[3], whose weighted mean value is 26435·5 J/g with a standard error of 1·0 J/g.

The work described above has been carried out as part of the research programme of the National Physical Laboratory, and this paper is published by permission of the Director of the Laboratory. I would like to thank Miss J. A. Nicholls who was responsible for the experimental work.

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VOL. 2 1961

KALORIMETRISCHE VERFAHREN BEI HÖHEREN TEMPERATUREN

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Bei kalorimetrischen Bestimmungen von Bildungswärmen, Wärmeinhalten und Umwandlungswärmen werden in der Regel diejenigen Verfahren bevorzugt, die eine Messung dieser Grössen bei Zimmertemperatur gestatten, weil diese Methoden sehr genaue Ergebnisse liefern und mit einem geringeren apparativen Aufwand auskommen. In manchen Fällen lassen sich diese bekannten und bewährten Verfahren[1–4] aber nicht in befriedigender Weise oder überhaupt nicht anwenden, so daß kalorimetrische Methoden bei höheren Temperaturen notwendig werden[5].

Bildungswärmen werden in der Regel nicht durch direkte Synthese, sondern indirekt aus Verbrennungs- und Lösungswärmen bestimmt. Dabei kann der Fall auftreten, daß die Bildungswärme als sehr kleine Differenz grosser Zahlen und daher auch bei großer Präzision der Messungen nur sehr ungenau bestimmt wird. Trotz der etwas geringeren Genauigkeit der Hochtemperaturkalorimeter (H.T.K.) kann dann ein anderer Reaktionsweg oder die direkte Synthese bei höheren Temperaturen zu besseren Ergebnissen führen. Insbesondere bei intermetallischen Verbindungen lassen sich vielfach bei Zimmertemperaturen keine brauchbaren Reaktionen auffinden, so daß systematische Untersuchungen nur durch Lösungskalorimetrie in flüssigen Metallen ausgeführt werden können. Manche Reaktionen, wie etwa die Mischung flüssiger Metalle, lassen sich überhaupt nur bei höheren Temperaturen verfolgen. Das gilt auch für den Übergang von durch Abschrecken erhaltenen Nichtgleichgewichten in thermodynamisches Gleichgewicht, wobei nicht nur die Wärmetönung, sondern auch die Kinetik von Interesse ist. Wärmeinhalte, spezifische Wärmen und Umwandlungswärmen können nach dem Mischungsverfahren (drop method) oder mit Oelsens Abkühlungskalorimeter prinzipiell nur dann einwandfrei gemessen werden, wenn die Umwandlungen bei der Abkühlung quantitativ ablaufen und die Probe sich nach vollständiger Abkühlung im thermodynamischen Gleichgewicht befindet. Wenn diese Bedingung nicht erfüllt ist, müssen die genannten Größen direkt bei höheren Temperaturen bestimmt werden. Direkte Messungen der wahren spezifischen Wärme bei höheren Temperaturen sind auch dann angebracht, wenn diese Größe sich aus Messungen des Wärmeinhaltes als Differentialquotient nicht mit ausreichender Genauigkeit ableiten läßt.

Mit diesen Beispielen ist der heutige Anwendungsbereich[1, 3–5, 8, 9, 89] der H.T.K. etwa umrissen. Die Technik der Kalorimetrie bei höheren Temperaturen bietet aber im Vergleich zu den bei Zimmertemperatur bekannten und üblichen Verfahren einige zusätzliche experimentelle Schwierigkeiten, die im folgenden kurz behandelt werden sollen. Ausserdem werden für alle Anwendungsbereiche die wichtigsten technischen Merkmale bewährter

Konstruktionen angegeben; eine ausführliche Darstellung aller bekannten Apparaturen soll an anderer Stelle erscheinen[6]. Wegen der einfacheren, aber zumeist auch weniger genauen Verfahren der Differentiellen Thermoanalyse (D.T.A.) sei auf eine Monographie von Smothers und Chiang[7] (mit 1546 Literaturzitaten bis 1957) verwiesen.

1. ALLGEMEINER TEIL

1.1. Die Kalorimetergleichung

In allgemeinen ist ein Kalorimeter ein zur Aufnahme eines Reaktionsgefässes bestimmter Hohlkörper, dessen Temperatur T_k entsprechend genau bestimmt werden kann. Im Kalorimeter kann elektrisch oder chemisch eine zeitlich variable oder konstante Wärmeleistung $L(z)$ (in W) entwickelt werden. Der Wasserwert (energy equivalent) ist eine temperaturabhängige Konstante $W(T)$, welche diejenige Wärmemenge (J/°C) bezeichnet, die notwendig ist, um bei adiabatischer Arbeitsweise, also ohne Wärmeaustausch mit der Umgebung, die Temperatur T_k des Kalorimeters um 1°C zu erhöhen. Das Kalorimeter ist von einem Thermostaten der konstant (oder nach einem bestimmten Programm variabel) geregelten Temperatur T_t umgeben. Eine weitere temperaturabhängige Apparatekonstante $K(T)$ bezeichnet den sekundlichen Wärmeaustausch des Kalorimeters mit dem Thermostaten (W/°C) bei einer Temperaturdifferenz von $T_k - T_t = 1$. Die in der Zeit dz dem Kalorimeter zugeführte Wärmemenge $L(z)dz$ wird dann gemäss der Kalorimetergleichung erster Näherung

$$L(z)dz = W(T)dT_k + K(T)(T_k - T_t)dz \qquad (1)$$

in zwei Anteile aufgespalten, nämlich in eine Erwärmung des Kalorimeters um dT_k und einen Wärmeaustausch mit dem Thermostaten.

Reaktionswärmen im Kalorimeter werden also aus dem beobachteten Verlauf von T_k und T_t, sowie den gesondert bestimmten Apparatekonstanten W und K als Integral über die nach Gl. (1) berechnete Leistung bestimmt.

Der häufigste Fall ist durch einen isothermen Thermostaten mit $T_t =$ konst gegeben. Befindet sich dabei das Kalorimeter zur Zeit $z = 0$ auf einer von T_t verschiedenen Anfangstemperatur T° und findet gemäss $L = 0$ keine Wärmeentwicklung statt, so folgt mit

$$W(T)dT_k = -K(T)(T_k - T_t)dz \qquad (2)$$

eine Temperaturänderung des Kalorimeters durch Wärmeaustausch mit der Umgebung. Für die zeitliche Anderung von T_k folgt dann mit

$$T_k = T_t + (T^\circ - T_t)\exp(-Kz/W) \qquad (3)$$

ein exponentieller Ausgleich der Temperaturen, dessen zeitlicher Verlauf durch die Zeitkonstante $\zeta_k = W/K$ gegeben ist. Bei Zimmertemperatur ist bei nicht zu kleinem Wasserwert W und, in der Regel, kleinem K die Zeitkonstante ζ_k sehr gross, so dass die Reihenentwicklung von Gl. (3) mit dem linearen Glied abgebrochen werden kann. Wir erhalten dann

$$T_k = T_t + (T^\circ - T_t)(1 - Kz/W) = T^\circ - (T^\circ - T_t)Kz/W \qquad (4)$$

VOL 2 1961

Werden alle τ_p sek äquidistante Ablesungen ausgeführt, so wird $z = n \,.\, \tau_p (n = 0,1,2,3..)$ und wir erhalten aus Gl. (4)

$$T_k = T^\circ - (T^\circ - T_t) n \, (\tau_p \, K/W) = T^\circ - (T^\circ - T_t) \, n \, k \qquad (5)$$

Die konventionelle thermochemische Abkühlungskonstante, k, ergibt sich also durch Einbeziehung der Dauer τ_p einer Ableseperiode in die Zeitkonstante τ_k gemäss

$$k = K, \tau_p / W = \tau_p / \tau_k \qquad (6)$$

Die Temperaturänderung ΔT_k in einer Ableseperiode wird als Gang bezeichnet. Bei der üblichen Auswertung wird allerdings die Anfangstemperatur T° nicht ganz konsequent durch die mittlere Temperatur in Vor- oder Nachperiode T_v oder T_n ersetzt, und anstelle der Thermostatentemperatur T_t eine rechnerische Konvergenztemperatur T_o eingeführt, in der auch der Einfluss von sekundären Effekten (z.B. Rühr- oder Verdampfungswärmen) enthalten ist. Wir erhalten dann für die Gänge in Vor- und Nachperiode

$$G_v = -k(T_v - T_o) \text{ und } G_n = -k(T_n - T_o) \qquad (7)$$

Bei höheren Temperaturen nimmt nun $K(T)$ schnell zu; als grobe Faustregel lässt sich eine Verdopplung für je 200°C annehmen. Die Forderung definierter Temperaturverteilung führt ausserdem zu kleinen Abmessungen und, in Verbindung mit den an sich schon geringen Wärmeinhalten metallischer Kalorimeter, zu kleinen Wasserwerten $W(T)$. Die Zeitkonstante τ_k wird also wesentlich kleiner, so dass die lineare Näherung Gl. (4) nicht mehr erlaubt ist. Wir erhalten dann aus Gl. (3)

$$\ln (T_k - T_t) = \ln (T^\circ - T_t) - nk \qquad (8)$$

Bei logarithmischer Darstellung resultiert daher ein linearer Verlauf, dessen Achsenabschnitt für $n = 0$ durch $\ln (T^\circ - T_t)$ und dessen Neigung durch k gegeben ist. Im Gegensatz zu Gl. (7) ist der logarithmische Gang also nicht mehr durch T°, sondern lediglich durch k bedingt.

1.2. Bestimmung der Konstanten k, K, und W

1.21. *Bestimmung von k*

Bei grossen Zeitkonstanten lässt sich k nach Gl. (7) aus dem Gang in der Vor- oder Nachperiode bestimmen. Da aber die rechnerische Konvergenztemperatur T_o nicht bekannt ist, wird sie eliminiert, so dass wir

$$k = (G_v - G_n)/(T_n - T_v) \qquad (9)$$

erhalten. Für sehr genaue Messungen empfiehlt sich die einfache Berechnung von G_v und G_n durch lineare Ausgleichsrechnung äquidistanter Werte.

Bei höheren Temperaturen und kleineren Zeitkonstanten muss dagegen die exponentielle Krümmung nach Gl. (3) und (8) berücksichtigt werden. T_t lässt sich dann aber nicht mehr in einfacher Weise eliminieren. Es ist

aber ohnehin erforderlich, die Messung erst einzuleiten, wenn sich nach Einbau einer Probe im Kalorimeter wieder ein thermisches Gleichgewicht eingestellt hat. Bei den in Frage kommenden kleineren Zeitkonstanten befindet sich dass Kalorimeter dann aber auch im Gleichgewicht mit dem Thermostaten, so dass T_t sich aus dem Mittelwert einer Anzahl von Ablesungen in der Vorperiode ergibt und in Gl. (8) eingesetzt werden kann; k folgt dann aus dem logarithmischen Gang nach Gl. (8).

Bei kleinen Zeitkonstanten ist die Genauigkeit von k vor allem durch die Schwankungen des Nullpunktes T_t begrenzt, woraus sich sofort die Notwendigkeit einer sehr konstanten Regelung von T_t ergibt. Dabei entsteht aber noch eine weitere für H.T.K. kennzeichnende Schwierigkeit. Wegen der zumeist kleinen Abmessungen des Kalorimeters ist der Wasserwert W_r des Reaktionsraumes nicht mehr klein im Vergleich mit $W(T)$, so dass die zweite Zeitkonstante W_r/K_r berücksichtigt werden muss und die Gleichung erster Näherung (1) das zeitliche Verhalten nicht mehr hinreichend genau beschreibt. In der Nachperiode macht dieser Umstand sich durch anfängliche Abweichungen vom logarithmischen Verlauf nach Gl. (8) bemerkbar, so dass k erst aus späteren, und damit auch kleineren und stärker durch die Nullpunktsschwankungen beeinträchtigten Ablesungen der Temperaturdifferenz $(T_k - T_t)$ bestimmt werden muss.

1.22. *Bestimmung von K*

Die Konstante K wird nach dem Verfahren der Gleichgewichtsleistung bestimmt[31]. Dazu wird das Kalorimeter bei konstantem T_t auf eine bestimmte höhere Temperatur T_k aufgeheizt, und eine Leistung L mit nur noch möglichst geringen Änderungen von T_k elektrisch erzeugt. Nach Einstellung des thermischen Gleichgewichts wird T_k als Mittelwert einiger äquidistanter Ablesungen bestimmt. Da im Gleichgewicht $dT_k = 0$, folgt aus Gl. (1)

$$K(T) = L/(T_k - T_t) \tag{10}$$

Zweckmässigerweise wird diese Bestimmung bei verschiedenen Werten von T_k und L ausgeführt und $K(T)$ durch lineare Ausgleichsrechnung ermittelt. In dieser Weise lässt sich gegebenenfalls auch feststellen, bis zu welchen maximalen Werten von $(T_k - T_t)$ die Temperaturabhängigkeit von $K(T)$ noch vernachlässigt werden kann[5].

Bei bekanntem k und W lässt sich zur Kontrolle K auch gemäss Gl. (6) berechnen.

1.23. *Bestimmung von W(T)*

Wenn K und k nach den vorstehenden Methoden bestimmt wurden, lässt sich $W(T)$ nach Gl. (6) zu $W(T) = K\zeta_p/k$ berechnen. Im allgemeinen muss $W(T)$ aber wesentlich genauer bestimmt werden, als es nach dieser Formel möglich ist. Bei adiabatischen Kalorimetern ergibt sich $W(T)$ definitionsgemäss als Verhältnis der auf elektrischem Wege zugeführten und genau gemessenen Wärmemenge und der adiabatisch bestimmten Temperaturerhöhung $T_e - T_a$. Vielfach besteht aber nicht die Möglichkeit einer hinreichend genauen adiabatischen Regelung. In

diesem Fall muss die mit dem Thermostaten der konstanten Temperatur T_t ausgetauschte Wärmemenge Q_a berücksichtigt werden. Diese ergibt sich aus den N Ablesungen in der Hauptperiode durch Integration des Wärmeaustauschgliedes der Gl. (1) $K(T_k - T_t)dz$ nach der Trapezregel zwischen der letzten Ablesung T_a der Vorperiode über die N Ablesungen T_n der Hauptperiode bis zur ersten Ablesung der Nachperiode T_e zu

$$Q_a = K\ [(T_a/2 + \Sigma T_n + T_e/2) - (N + 1)T_t]\ \zeta_p \qquad (11)$$

In der Regel wird aber nicht K nach Abschnitt **1.22**, sondern $k = K\zeta_p/W$ aus den Gängen nach Abschnitt **1.22** bestimmt. Durch Division von Gl. (12) mit $W(T)$ führen wir statt $K\zeta_p$ die Konstante k ein, was eine Umrechnung von Q_a auf eine Korrektur der Temperaturänderung ΔT bedeutet. So erhalten wir

$$Q_a/W = \Delta T = k[T_a/2 + \Sigma T_n + T_e/2 - (N + 1)T_t] \qquad (12)$$

Ausserdem muss T_t durch die rechnerische Konvergenztemperatur T_o ersetzt, und diese nach Gl. (7) eliminiert werden. Mit

$$kT_o = G_v + kT_v = G_n + kT_n \qquad (7a)$$

erhalten wir dann aus Gl. (12) die beiden Formen der Regnault–Pfaundler-Korrektur

$$\begin{aligned}\Delta T &= k\,[T_a/2 + \Sigma T_n + T_e/2 - (N + 1)T_v] - (N + 1)G_v \\ &= k\,[T_a/2 + \Sigma T_n + T_e/2 - (N + 1)T_n] - (N + 1)G_n \qquad (13)\end{aligned}$$

Der zweite Ausdruck bietet den Vorteil, dass k mit einer kleineren Zahl multipliziert wird. Es empfiehlt sich aber, die Berechnung ausserdem nach der ersten Form auszuführen, was bei einer geringen Vermehrung des Rechenaufwandes eine Kontrolle der Rechnung erlaubt.

Bei höheren Temperaturen wird bei hinreichend kleinen Zeitkonstanten T_t in der Regel aus dem Mittelwert der konstanten Ablesungen in der Vorperiode bestimmt. Man kann nun wahlweise nach Abschnitt **1.21** die Konstante k aus dem logarithmischen Gang nk in der Nachperiode nach Gl. (8) ableiten und aus Gl. (12) die Korrektur der Temperaturerhöhung berechnen, oder K nach Abschnitt **1.22** bestimmen und dann nach Gl. (11) direkt die ausgetauschte Wärmemenge Q_a ableiten und als Korrektur an der gemessenen Wärmetönung anbringen.

Macht sich in der Nachperiode die zweite Zeitkonstante des Reaktionsgefässes $\zeta_{kr} = W_r/K_r$ derart bemerkbar, dass der lineare Verlauf nach Gl. (8) sich nicht einstellt, so empfiehlt sich eine andere Auswertung. Dazu wird die Temperatur des Kalorimeters T_k in äquidistanten Ablesungen bis zur Einstellung des thermischen Gleichgewichts verfolgt und die Reaktionswärme ausschliesslich nach Gl. (11) als mit dem Thermostaten ausgetauschte Warmemenge Q_a bestimmt, wozu natürlich eine vorherige Messung von K nach Abschnitt **1.22** erforderlich ist. Dieses Verfahren ist vor allem bei kleinen Zeitkonstanten praktikabel, weil die Messgenauigkeit durch die Schwankungen des Nullpunktes beeinträchtigt wird, und

daher die Streuungen umso kleiner werden, je schneller der Versuch abläuft. In dieser Weise lassen sich natürlich nur Wärmetönungen, aber keine Wasserwerte bestimmen. Der Wasserwert kann aber mit Vorteil als kleine Korrektur verwendet werden, wenn sich das Kalorimeter nur langsam mit dem Thermostaten ins Gleichgewicht setzt. Es genügt dann, das Produkt dieser kleinen Temperaturdifferenz mit dem Wasserwert als Korrektur an Q_s anzubringen, wozu auch ein näherungsweise gemäss $W = K\zeta_p/k$ abgeleiteter Wasserwert ausreicht.

Normalerweise wird aber die nach Gl. (12) oder (13) bestimmte Korrektur ΔT an der Differenz der ersten und letzten Ablesung $T_e - T_a$ angebracht, so dass sich nach Division der elektrisch gemessenen und dem Kalorimeter zugeführten Wärmemenge mit der korrigierten Temperaturerhöhung der Wasserwert ergibt.

Ebenso erhalten wir die unbekannten Reaktionswärmen durch Multiplikation des zuvor bestimmten Wasserwertes mit der korrigierten Temperaturänderung. Bei kleinen Kalorimetern, wie sie vielfach bei höheren Temperaturen verwendet werden, muss natürlich der erhebliche Einfluss des Wärmeinhaltes der im Kalorimeter befindlichen Probe auf den Wasserwert berücksichtigt und bestimmt werden, so dass bei Beschikkung mit Proben anderen Wärmeinhaltes eine neue Bestimmung von W erforderlich ist.

VOL
2
1961

1.3. Die prinzipiellen Möglichkeiten kalorimetrischer Verfahren

Die vorstehenden Ausführungen bezogen sich überwiegend auf den häufigsten Fall der Erwärmungskalorimetrie, bei dem in einem isothermen Thermostaten der zeitliche Verlauf von T_k verfolgt wird. In älteren Darstellungen findet man für dieses Verfahren gelegentlich die Bezeichnung 'isotherme Kalorimetrie', etwas irreführend, weil T_t, nicht aber T_k konstant ist; als isotherm werden wir nur Kalorimeter bezeichnen, bei denen T_k konstant ist.

Bei der Entwicklung von Hochtemperaturkalorimetern nach dem Erwärmungsprinzip war vor allem die noch nicht geklärte Frage von Interesse, bis zu welchen Temperaturen dieses Verfahren überhaupt angewendet werden kann. Inzwischen konnten wir die Brauchbarkeit dieser Methode für Genauigkeiten von augenblicklich 1–2 Prozent bei 975°C nachweisen ($K = 1{\cdot}05$ W/°C, $W = 315$ J/°C, $\zeta_k = 300$ sec). Der Anwendungsbereich lässt sich aber voraussichtlich auf noch höhere Temperaturen und kleinere Zeitkonstanten ausdehnen.

Bei höheren Temperaturen nimmt die Genauigkeit der Erwärmungskalorimetrie ab, weil der Anteil des Wärmeaustausches zunimmt und, wegen der Nullpunktsschwankungen und des schnellen Temperaturausgleichs, k nicht mehr so genau bestimmt werden kann. Es wäre zunächst denkbar, durch adiabatisches Arbeiten den Wärmeaustausch zu unterdrücken, was aber zu prinzipiellen Schwierigkeiten führt und einen wesentlich höheren Regelaufwand (P.I.D.-Regler) bedingt als die isotherme Regelung, die sich auch bei sehr hohen Temperaturen mit einfachen P-Reglern beherrschen lasst. Eine andere Überlegung beruht darauf, dass die Wärmeentwicklung $L\mathrm{d}z$ nach Gl. (1) in zwei Anteile, nämlich

der Erwärmung des Kalorimeters und des Wärmeaustausches mit dem Thermostaten zerlegt wird, und der zweite Anteil auf Kosten des ersten bei höheren Temperaturen schnell zunimmt. Es liegt daher näher, den grösseren Anteil des Wärmeaustausches nicht durch adiabatisches Arbeiten zu unterdrücken, sondern zur eigentlichen Messgrösse zu machen und isotherm mit Wärmeströmungskalorimetern zu arbeiten. Dabei lässt sich K durch direkte elektrische Eichung nach **1.22** bestimmen, so dass die dann ungenauere Ableitung von k nach **1.21** entfällt. Wir haben ausserdem mit der Möglichkeit zeitlicher Änderungen von K gerechnet und daher ein automatisches Kompensationsverfahren entwickelt. Bei dieser Methode wird bei konstanter Leistung L mit einem Temperaturregler eine konstante Temperaturdifferenz $T_k - T_t$ bei konstantem T_t eingestellt, so dass Reaktionswärmen als Differenzen der summierten Einschaltzeiten der Leistung L bestimmt werden können. Dieses Verfahren lässt sich mit Genauigkeiten von 1 Prozent bis augenblicklich 1000°C anwenden und dürfte auch bei wesentlich höheren Temperaturen ebenso brauchbar sein, weil es keine temperaturabhängigen Voraussetzungen enthält. Isotherme Verfahren bieten den weiteren Vorteil, dass die Temperaturabhängigkeit von $K(T)$ ausgeschaltet wird.

Wir wollen aber zunächst einmal die prinzipiellen Möglichkeiten kalorimetrischer Verfahren betrachten. Die historisch bedingte Benennung, wie etwa Eiskalorimeter oder Verbrennungskalorimeter, bezieht sich nur auf einzelne und nicht vergleichbare Merkmale und lässt daher die Wirkungsweise des kalorimetrischen Verfahrens nur ungenügend erkennen. Es ist besser, von der Kalorimetergleichung (1) auszugehen, in die neben den Konstanten W und K und der Versuchsdauer z die Variablen L, T_k und T_t eingehen. Die verschiedenen Möglichkeiten einer kalorimetrischen Messung ergeben sich dann aus der Auswahl des Mess- und Regelprogramms dieser Variablen.

Gleichung (1) zeigt nun die erwähnte Aufspaltung der Wärmemenge $L\mathrm{d}z$ in die Erwärmung des Kalorimeters $W\mathrm{d}T_k$ und den Wärmeaustausch $K(T_k - T_t)\mathrm{d}z$. Daraus folgt sofort die Möglichkeit, entweder den ersten Anteil durch isothermes Arbeiten wegen $\mathrm{d}T_k = 0$, oder den zweiten Anteil durch adiabatisches Regeln von T_t gemäss $T_t = T_k$ zu unterdrücken oder zu einer kleinen Korrektur zu machen. Ausserdem kann die Leistung $L = 0$ gewählt werden, so dass nach Gl. (2) die Temperaturänderungen nur noch durch den Wärmeaustausch bedingt sind. Bei einem isothermen Thermostaten führt das zu dem durch Gl. (2)–(5) gegebenen Temperaturausgleich. Bei variablem T_t besteht ausserdem die Möglichkeit einer Wärmezufuhr, die durch $K(T_k - T_t)\mathrm{d}z$ gegeben ist. Auf diesem Prinzip beruhen die bekannten Abkühlungs- und Erwärmungsverfahren zur Bestimmung von wahren spezifischen Wärmen und Umwandlungswärmen. Ein ganz anderes Verfahren stellen die Umwandlungskalorimeter dar, bei denen $T_k = T_t = T_u$ (Umwandlungstemperatur). Wegen $\mathrm{d}T_k = 0$ und $T_k - T_t = 0$ ist sowohl die isotherme als auch die adiabatische Bedingung wenigstens näherungsweise erfüllt. Die Leistung L ergibt sich dann aus der Umwandlungswärme und dem Umsatz.

Im Folgenden sollen nun die prinzipiellen Möglichkeiten erörtert werden, die sich ergeben, wenn bei konstantem oder nach einem vorgegebenen

Programm variabel geregeltem T_t der Kalorimetertemperatur T_k verschiedene Bedingungen auferlegt werden. Vergleichsweise einfach zu realisieren sind die Verfahren der ersten Gruppe, bei denen T_t konstant ist.

1.31. *Verfahren mit konstanter Temperatur des Thermostaten* T_t

1.311. T_k *ebenfalls konstant*

1.3111. $T_k = T_t$ (*Isotherm-adiabatisch*)—Diese Bedingung läßt sich in einfacher Weise mit Umwandlungskalorimetern, insbesondere dem Verdampfungskalorimeter, realisieren, bei denen $T_k = T_t = T_u$ der betreffenden Umwandlungstemperatur gewählt wird. Regelung von T_u über den Druck ermöglicht Anwendungen auf organische Reaktionen[12–20] und gegebenenfalls eine einfachere Apparatur[21]. Die Leistung L kann konstant oder variabel sein; bei Gasreaktionen über Katalysatoren hat sich jedoch Messung bei konstantem Gasstrom und konstantem Umsatz als zweckmäßig erwiesen. Der Wasserwert W braucht nicht sonderlich genau bekannt zu sein, weil er wegen $dT_k = 0$ entweder überhaupt nicht in die Rechnung eingeht oder bei geringen Abweichungen von T_k = konst nur als kleine Korrektur auftritt. Die Leistung L ergibt sich nicht nach Gleichung (1), sondern aus der Umsatzgeschwindigkeit dN/dz und der Umwandlungswärme, die entsprechend genau bestimmt werden müssen.

1.3112. $T_k - T_t = Konstant$ (*Isotherm*)—Eine zweite Möglichkeit[5, 22] ergibt sich, wenn eine elektrisch erzeugte und entsprechend genau gemessene, am besten konstante Leistung L mit einem Temperaturregler so gesteuert wird, daß die Temperaturdifferenz $T_k - T_t$ konstant wird. Das Verfahren läßt sich mit einer Genauigkeit von etwa 1 Prozent zweckmäßigerweise so ausführen, daß L elektronisch konstant gehalten wird und die Temperaturregelung mit einem Modulationsregler erfolgt, dessen Modulationsperiode τ_m in der Größenordnung einiger ganzzahliger Sekunden liegt. Die damit synchronisierte Beobachtungsperiode τ_p wird als ganzzahliges Vielfaches von τ_m gemäß $\tau_p = n\tau_m$ gewählt, wobei für n Werte von etwa 20 zweckmäßig sind, um Streuungen auszugleichen. Am Ende jeder Beobachtungsperiode wird die mit einer Additionsstopuhr oder einem Counter integrierte gesamte Einschaltzeit τ_e der elektrischen Heizung abgelesen oder registriert, so daß der gesamte Wärmeaustausch zwischen Kalorimeter und Thermostat in der Beobachtungsperiode sich aus $Q_p = L\tau_e$ ergibt. Reaktionswärmen Q_r folgen dann aus den Differenzen der in der Vorperiode als konstant bestimmten Q_p und den sich automatisch in der Hauptperiode anders einstellenden Einschaltezeiten τ_e' gemäß $Q_r = L(\tau_e - \tau_e') = Q_p - L\tau_e'$, wodurch die kalorimetrische Messung sich in einfacher Weise auf äquidistante Registrierung der summierten Einschaltzeiten reduziert. Das Verfahren bietet den weiteren Vorzug, daß durch entsprechende Wahl von L und $(T_k - T_t)$ eine Anpassung an die Größe der Reaktionswärme möglich ist und positive wie negative Reaktionswärmen in derselben Weise gemessen werden. Der Wasserwert tritt ebenfalls nur als Korrektur für Abweichungen von T_k = konst. in Erscheinung. Genauigkeit und Empfindlichkeit sind durch die Unsicherheit der Konstanz der Temperatur des Thermostaten gegeben. Das

VOL. 2 1961

Verfahren dürfte vor allem für höhere Temperaturen von Bedeutung sein, bei denen die einfachere Erwärmungsmethode wegen hoher K-Werte und schnellen Temperaturabfalls in der Nachperiode zu ungenau wird.

Eine weitere, spezielle Möglichkeit[31] ergibt sich bei der Bestimmung von Schmelzwärmen, wobei die Abkühlung der flüssigen Probe in einem Ofen konstanter Temperatur T_t bis zum Erstarrungspunkt verfolgt wird, so dass die Bedingung $T_k = T_u = \text{konst}$ sich aus der isothermen Umwandlung ergibt. Die Umwandlungswärme folgt dann aus der zuvor nach **1.22** bestimmten Konstanten K, der gemessenen Temperaturdifferenz $T_k - T_t$ und der Dauer des Haltepunktes z_h gemäss $Q_u = K(T_k - T_t)z_h$.

1.312. *T_k variabel*

Wenn in einem Erwärmungskalorimeter eine konstante oder variable Leistung L nur für eine bestimmte Dauer erzeugt wird, so resultiert eine durch die Zeitkonstanten des Kalorimeters gegebene zeitliche Änderung der Kalorimetertemperatur T_k. Aus dem beobachteten Verlauf von T_k läßt sich näherungsweise der zeitliche Verlauf von $L(z)$ rekonstruieren[10, 11]. Die entwickelte Wärmemenge wird nach Gleichung (1) in zwei Anteile zerlegt, nämlich Erwärmung des Kalorimeters und Wärmeaustausch mit dem Thermostaten. Mit höheren Temperaturen und zunehmenden $K(T)$, sowie bei längerer Dauer der Wärmeentwicklung nimmt der Beitrag des Wärmeaustausches im Vergleich zum Anteil der Erwärmung schnell zu, so daß der zweite Anteil entsprechend genau bestimmt werden muß. Er kann durch adiabatisches Arbeiten unterdrückt und klein gehalten werden. Wenn der Anteil des Wärmeaustausches aber überwiegt, kann es zweckmässiger sein, umgekehrt die Erwärmung des Kalorimeters zu unterdrücken und die unter **1.1** erwähnten Methoden mit $dT_k = 0$ zu verwenden.

Die Auswertung der Gleichung (1) hat bei einem Erwärmungskalorimeter die Bestimmung der beiden Apparatekonstanten W und K zur Voraussetzung. W wird in üblicher Weise durch elektrische Eichung nach **1.23** bestimmt. Neue Kalorimeter sollten grundsätzlich auf mögliche Abhängigkeit des Wasserwertes von Dauer und Größe der Leistung L geprüft werden[23]. Diese Möglichkeit entfällt bei der gelegentlich angewandten Eichung durch Einwurf einer auf höhere Temperatur vorgeheizten Probe (Thermophor). Letzteres Verfahren ist aber schon darum weniger zuverlässig, weil der Wärmeinhalt der Probe nicht mit derselben Genauigkeit bekannt ist wie der einer elektrisch erzeugten Wärmemenge und weil der Wärmeverlust der Probe beim Einwurf in das Kalorimeter sich nur schwer überprüfen läßt. Die elektrische Eichung verbürgt eine weit höhere Zuverlässigkeit der Absolutwerte.

Die Bestimmung von K oder k erfolgt nach Abschnitt **1.21** und **1.22.**

Wird der Wasserwert des Kalorimeters kleiner gehalten als der Probe, so lassen sich durch elektrische Bestimmungen des Wasserwertes des leeren und des mit der Probe beschickten Kalorimeters die spezifischen Wärmen der Probe bei verschiedenen Temperaturen unmittelbar bestimmen[24, 25]. Dieses Verfahren wurde bisher als nur für Temperaturen bis etwa 300°C brauchbar angesehen, konnte aber neuerdings auch bis 1300°C angewendet werden[26].

1.32. *Verfahren mit variablem* T_t

Bei diesem Verfahren wird die Temperatur des Thermostaten nach irgendeinem Programm geregelt, wofür entweder gleichmäßige Erwärmung oder Abkühlung oder adiabatische Steuerung in Frage kommt, bei der gemäß $T_t = T_k$ der zeitliche Verlauf von T_t durch das Programm von T_k oder umgekehrt gegeben ist. Wir erhalten in dieser Gruppe daher folgende Möglichkeiten.

1.321. $T_k = T_t$ (*Adiabatisch*)

Dies entspricht dem häufigen Fall einer adiabatischen Regelung, die sich mit heutigen Mitteln automatisch mit großer Genauigkeit erreichen läßt. Nach Gleichung (1) wird dann der Anteil des Wärmeaustausches zumindest sehr klein, so daß die Unsicherheit des K-Wertes keinen sonderlichen Einfluß ausüben kann. Das adiabatische Prinzip muß aber trotzdem kritisch und mit Vorsicht angewandt werden: es ist umso unsicherer, an je weniger Stellen die Temperaturdifferenz $T_k - T_t$ gemessen wird. Vor allem bei plötzlich einsetzenden Reaktionen und entsprechender Erwärmung des Kalorimeters ist es keineswegs selbstverständlich, daß der zeitliche Temperaturverlauf im Kalorimetermantel undim adiabatisch nachgesteuerten Thermostaten überall und regelmässig reproduzierbar wenigstens im Mittel der adiabatischen Bedingung genügt. Es besteht dann die Möglichkeit, daß die Unsicherheit des K-Wertes zwar eliminiert, dafür aber eine größere und zudem nicht nachprüfbare Unsicherheit des zweiten Faktors $(T_k - T_t)$ eingeführt wird. Wesentlich günstiger sind dagegen die Verhältnisse bei stetigen Temperaturänderungen, wie sie bei der Bestimmung von spezifischen Wärmen durch adiabatisches Aufheizen gegeben sind. Aber auch in diesem Fall sind eine Anzahl von Vorsichtsmassnahmen zu beachten. Die relativ sicherste Methode einer Nachprüfung besteht darin, die spezifischen Wärmen bei verschiedenen Aufheizgeschwindigkeiten zu messen. Gleichung (1) zeigt nämlich, daß bei Abweichungen von der adiabatischen Bedingung die Ergebnisse von der Versuchsdauer abhängen müssen. Es empfiehlt sich ausserdem, bei einer Kontrollmessung durch ein verschiebbares Thermoelement das Kalorimeter auf uniforme Temperaturverteilung hin zu prüfen, besonders wenn es aus dünnen Blechen konstruiert wird, um einen möglichst kleinen, für die Messgenauigkeit an der Probe günstigen Wasserwert des leeren Kalorimeters zu erzielen. Nach unseren Erfahrungen können nämlich bei unzweckmässiger Anordnung der elektrischen Heizwicklungen im Kalorimeter Ueberhitzungen begrenzter Teile auftreten, die Absolutfehler von einigen Prozent bei Reproduzierbarkeit der Messung von einigen Zehntelprozent verursachen können. Der Einfluß von Abweichungen vom adiabatischen Verhalten läßt sich übrigens weitgehend dadurch eliminieren, daß die Messungen mit leerem und vollem Kalorimeter möglichst mit derselben Aufheizgeschwindigkeit ausgeführt werden, was allerdings im Bereich von Phasenumwandlungen nicht immer erreichbar ist.

Der Einfluß von Überhitzung ist dagegen viel schwieriger zu beseitigen, weil er mit der Größe der Leistung L zunimmt, und diese bei gleicher Aufheizgeschwindigkeit im vollen Kalorimeter wesentlich größer sein muß. Es muß daher bei jedem Kalorimeter eine zweckmäßige Anordnung der Heizelemente gefunden (und kontrolliert) werden, die Überhitzung

VOL. 2 1961

einzelner Stellen ausschließt, besonders bei kleinem Wasserwert des Kalorimeters. Neuerdings ist es gelungen, durch adiabatische Aufheizung Messungen bei Temperaturen bis 1600°C auszuführen[28].

Wird die Probe vom Kalorimeter aus beheizt, so bleibt ihre Temperatur hinter der seinigen zurück, d.h. die spezifische Wärme wird bei einer tieferen Temperatur bestimmt. Diese Verzögerung vermindert sich durch besseren Wärmeausgleich bei höheren Temperaturen, so daß sich eine etwas schnellere Erwärmung der Probe als im Kalorimeter ergeben wird, was bei der Berechnung der spezifischen Wärmen u.U. berücksichtigt werden muß. Zwar besteht ein Verfahren zur Berechnung der thermischen Verzögerung[28], es ist aber sicherer, die Temperatur sowohl im Kalorimeter wie in der Probe zu messen.

1.322. $T_k = konst. = T_u$ (*Isotherm*)

Dieser Sonderfall tritt bei der Bestimmung von isothermen Umwandlungswärmen auf. Es gibt hier mehrere experimentelle Möglichkeiten, je nachdem, ob die Umwandlung bei sich abkühlendem oder bei aufgeheiztem Thermostat verfolgt wird.

1.3221. *Bestimmung der Umwandlungswärme aus der Dauer des Haltepunktes*—Die Umwandlungswärme einfach proportional der Dauer des Haltepunktes zu setzen[29], kann offensichtlich nicht richtig sein, weil die Temperaturdifferenz $T_k - T_t$ mehr oder weniger linear mit der Zeit variiert. Eine korrekte Formel wurde aus Gl. (1) abgeleitet[30]. Die Eichung erfolgt durch Vergleich mit bekannten Umwandlungswärmen. Dabei wird vorausgesetzt, daß $K(T)$ bei Verwendung eines zweiten Tiegels und meistens bei etwas anderer Temperatur (!) denselben Wert wie bei der Eichung annehmen wird, was sicher eine grobe, nicht nachprüfbare Fehlerquelle darstellt. Zumindest müßte $K(T)$ bei verschiedenen Temperaturen bestimmt werden.

1.3222. *Direkte elektrische Eichung*—Bei reproduzierbarer Erwärmung des Thermostaten, beispielsweise durch konstante Regelung der Leistung eines Ofens[32], ist am Haltepunkt das Integral über $(T_k - T_t)dz = F(0)$ ein Maß für die Umwandlungswärme, und $Q_u = KF(0)$. Die Bestimmung von K kann dadurch umgangen[33] werden, daß bei einer zweiten Messung ein Teil der Schmelzwärme mit einer Eichheizung erzeugt und genau gemessen wird; da jetzt nur ein Teil der Schmelzwärme von aussen zugeführt werden muß, ist die zweite Fläche $F(Q)$ kleiner, gemäß $Q_u - Q_e = KF(Q)$. Daraus folgt

$$Q_u = Q_e F(0)/\,[F(0) - F(Q)]$$

1.323. T_k *variabel*

Eine wohl mehr qualitative Messung der spezifischen Wärmen nach den Methoden der D.T.A. ist möglich, wenn bei gleichmäßiger Aufheizung des Ofens T_k und T_t bestimmt werden. Eichung erfolgt durch Vergleich mit Proben genau bekannter (?) spezifischer Wärme, wobei dieselben Einwände wie unter **1.3221** gelten[34–36]. Besser wäre eine direkte Bestimmung von K nach Abschnitt **1.22.**

1.4. Apparative Ausrüstung

Bei hohen Temperaturen müssen im wesentlichen dieselben Messungen ausgeführt werden wie bei Zimmertemperatur. So werden bei elektrischen Eichungen Strom, Spannung und Zeit bei Genauigkeiten bis 0,5 Prozent mit Zeigerinstrumenten der Güteklasse 0·2, bei höheren Ansprüchen an Genauigkeit mit Kompensationsapparaten gemessen; es gibt auch halbautomatische Schaltungen[37, 38]. Die absolute Temperatur wird entweder mit Widerstandsthermometern oder mit Thermoelementen bestimmt, deren kalte Lötstellen für genaue Messungen in einem gerührten Eisbad angebracht werden müssen[23]. Für die Messung der Temperaturdifferenz $T_k - T_t$ sind Differentialthermoelemente zweckmäßig. Die Messgenauigkeit wird bei Widerstandsthermometern bei höheren Temperaturen wohl durch die Schwierigkeit eines hinreichend konstanten Wertes des Isolationswiderstandes, und bei Thermoelementen vor allem durch die parasitären Thermokräfte begrenzt. Nach unserer Erfahrung führen Temperaturschwankungen im Labor während einer Messung zu merklich stärker streuenden Messwerten. Zu beachten ist ausserdem, daß gemäß Gl. (1) in der Regel eine Messung nur der Temperaturdifferenz $T_k - T_t$ nicht ausreicht und die absolute Temperatur T_k oder T_t gleichfalls mit entsprechender Genauigkeit bekannt sein muß. Bei Reaktionswärmen sind geringe Abweichungen von der Temperaturskala in der Regel ohne Belang, in die spezifische Wärme geht sie aber genauigkeitsbestimmend ein und muß daher im ganzen Temperaturbereich durch entsprechend präzise Eichung bestimmt werden. Mit gealterten Pt–Pt,Rh–Thermoelementen ist eine Eichung mit Kompensationsapparaten bei genau bekannten Fixpunkten auf 0·1°C möglich, unedle Thermoelemente[39] zeigen aber schon nach einmaliger Erhitzung auf 900° Aenderungen von *ca.* 1°C.

Bei komplizierten Apparaturen besteht die prinzipielle Schwierigkeit, daß neben Heizspannungen der Größenordnung 10^2 V Thermospannungen auf 10^{-7} V genau gemessen werden müssen. Die demnach erforderlichen Isolationswiderstände können aber schon ab *ca.* 600–700°C nicht mehr realisiert werden; Kriechströme lassen sich durch Erdung von Kalorimeter und Thermostat sowie durch Abschirmung der Zuleitungen und Aufstellung der Kompensatoren auf geerdete Aluminiumbleche unterbinden[23, 40]. Ein neues Kalorimeter sollte dahingehend geprüft werden, daß Ein- oder Ausschalten irgend eines Kreises keine bleibende Aenderung oder gar ständige Schwankungen der Anzeige eines Galvanometers hervorruft; kurze induktive Stösse sind dagegen zumeist harmlos. Widerstandsthermometer werden in Verbindung mit den bekannten Brücken- oder Kompensationsschaltungen verwendet, wobei die Anforderungen an die Temperaturkonstanz der Messbrücken geprüft werden müssen. Thermokräfte werden mit thermokraftarmen Kompensatoren nach Diesselhorst gemessen, konstante Temperaturen können mit Stöpselwiderständen vorgegeben werden (einfache Kompensationsschaltung[33]). Gleichstromverstärker sind bequemer, in der Regel aber um eine Größenordnung ungenauer als einfache Galvonometer mit entsprechendem Lichtweg. Bei Temperaturen bis vielleicht 500°C können mehrere Kompensationswiderstände hintereinandergeschaltet werden, bei höheren muß aber jeder

VOL. 2 1961

Kompensationskreis getrennt aufgebaut werden, um eine gegenseitige Beeinflussung der Anzeige zu vermeiden[23].

Als Öfen werden in der Regel die üblichen mit einer Heizwicklung versehenen keramischen Rohre verwendet, für höhere Temperaturen sind aber auch Molybdänrohr-[26] und sogar Tammann-Öfen brauchbar[33]. Als Werkstoffe können Aluminium–Kupfer–Bronze oder zunderfreie Stähle verwendet werden, wobei sich aber oberhalb von 600°C immer ein Schutzgas empfiehlt. Bei Legierungen müssen Konzentrationen und Temperaturen gemieden werden, bei denen langsame Umwandlungen auftreten, insbesondere Ausscheidungsvorgänge, weil sie zu mangelhaft reproduzierbaren Wasserwerten führen können. Umwandlungen im Werkstoff des Kalorimeters beeinträchtigen natürlich die Genauigkeit von Messungen der spezifischen Wärme.

1.5. Hochtemperaturthermostaten

Die Erfahrung hat gezeigt, daß die Genauigkeit einer kalorimetrischen Messung bei hohen Temperaturen in erster Linie von der Güte der Temperaturregelung abhängt. Elektrisch eichbare H.T.K. wurden erst durch die Entwicklung von auf einigen tausendstel Grad konstanten Thermostaten möglich. Konstanz der Temperatur läßt sich mit folgenden Mitteln erreichen.

1.51. *Konstant geregelte Spannung*

Die einfachste Methode besteht in der Verwendung einer mit Thyratrons oder Magnetverstärkern genau geregelten Spannung, mit der Ofen oder Thermostat betrieben werden. Dabei ist aber zu bedenken, daß je nach Ofencharakteristik eine Spannungskonstanz von etwa 0·1 Prozent bei 500°C eine Temperaturkonstanz von nur etwa 0·5°C einbringt. Eine Dämpfung nach dem Tianschen Prinzip (unter **1.3**) ist daher erforderlich. Genaue Programmregelungen lassen sich so nicht verwirklichen.

1.52. *Siedepunktthermostaten*

Diese sind naturgemäß besonders zweckmäßig bei Verdampfungskalorimetern[12–21]. Die Temperatur kann zusätzlich über den Druck geregelt werden. Nachteilig ist der beschränkte Temperaturbereich: Programmregelungen über große Temperaturintervalle sind ausgeschlossen.

1.53. *Schachtelthermostaten nach Tian*

Wenn periodische Temperaturschwankungen mit einer Austauschkonstante K auf einen gut temperaturleitenden Körper des Wasserwertes W übergehen, werden sie im Verhältnis W/K gedämpft. Durch Ineinanderschachteln von drei Ausgleichskörpern[41, 42] konnten so die äusseren periodischen Schwankungen von etwa 1 Prozent auf einige tausendstel reduziert werden. Derselbe Effekt wird übrigens benutzt, wenn die Temperatur des Kalorimeters mit einem Differentialthermoelement nicht gegen den Thermostaten, sondern gegen einen Ausgleichskörper gemessen wird. Solche Anordnungen sind eigentlich keine Differentialkalorimeter, sondern Tian-Thermostaten.

Nachteilig sind die recht großen Abmessungen solcher Thermostaten und ihre sehr träge Einstellung nach Störungen des thermischen Gleichgewichts, etwa nach Einbau einer Probe in das Kalorimeter. Zudem können sie natürlich nicht die manchmal recht erhebliche Wärmeabgabe des Kalorimeters an den Thermostaten ausregeln, so daß die Temperaturkonstanz nur vor der Messung gegeben ist und während deren Dauer Verschiebungen um einige hundertstel Grad möglich sind[23]. Programmregelungen sind ebenfalls ausgeschlossen. Ausserdem ist die Dämpfung umgekehrt proportional zu K, das sich aber erfahrungsgemäß bei einer Temperaturerhöhung um 200°C etwa verdoppelt, so daß die Dämpfung eines dreiteiligen Thermostaten in diesem Intervall um den Faktor 8 vermindert werden würde; dieser Verschlechterung kann allerdings durch den Einbau von Strahlungsblechen (convection shield) begegnet werden. Systematische Abweichungen vom Sollwert, die bei Fallbügelregler durchaus in der Größenordnung von 1°C liegen, können natürlich ebenfalls nicht ausgeregelt werden und führen daher zu systematischen Abweichungen des Thermostaten vom Sollwert.

1.54. *Modulationsregler nach Wittig, Schilling und Kemeny*

Sogenannte Zweipunktregler, wie die bekannten Fallbügelregler, führen prinzipiell zu Regelschwingungen, deren Amplitude etwa proportional der Leistungsdifferenz beider Arbeitsstufen und der Totzeit sind, die beide nicht unter ein bestimmtes Maß herabgesetzt werden können. Die Regelschwingungen lassen sich aber durch die Verwendung von P-Reglern, wie etwa Thyratron- oder Magnetverstärkerschaltungen, vermeiden, die aber nur bei sehr kleinen Totzeiten und Zeitkonstanten angebracht sind, da sie Impulse der Grössenordnung von 0·01 sec liefern. Bei den meist sehr großen Totzeiten thermischer Anordnungen von *ca.* 10 sec genügen aber Impulse von einigen Sekunden, die man einfacher und billiger durch die sogenannte Linearisierung des Zweipunktreglers zu einem P-Regler erhält, wofür der bekannte Gouy-Modulator ein einfaches Beispiel darstellt[42]. Bei diesen Modulationsreglern wird durch einfache periodische Relativbewegung der Sollwertmarke und der Anzeige des Ist-Wertes ganz ähnlich wie bei der Steuerung eines Thyratrons das Verhältnis der Ein- und Ausschaltezeiten der elektrischen Leistung proportional zu den momentanen Abweichungen vom Sollwert verstellt. Diese Modulation läßt sich mit einfachen Mitteln durch Oszillation einer Photozelle oder durch periodische Abblendung des Lichtzeigers erzielen. Es wurde ausserdem eine rein elektronische Schaltung entwickelt, bei der Steuerimpulse erzeugt werden, deren zeitlicher Abstand über zwei durch Photozellen gesteuerte Kippkreise je nach Stand des Lichtzeigers geregelt wird, wodurch eine Linearisierung ohne Modulation ermöglicht wird[44].

Von anderer Seite[45] wurde eine Einschleusung einer periodisch oszillierenden Spannung in den Thermoelement–Galvanometer-Kreis vorgeschlagen, was für Öfen durchaus brauchbar sein mag. Bei sehr genauen Temperaturregelungen bestehen aber offensichtlich die Gefahren parasitärer Thermokräfte und von Komplikationen durch Anregung des Galvanometers zu periodischen Schwingungen.

VOL. 2 1961

1.55. *Der Doppelthermostat*

Mit den unter **1.54** beschriebenen Reglern kann jeder beliebige elektrische Ofen mit einfachen Galvanometern (z.B. Typ RSG 8 von Ruhstrat, Göttingen) mit einem Lichtzeiger von nur 50 cm auf etwa 0·1 °C konstant gehalten werden, so daß durch den Tianschen Effekt die Temperaturschwankungen im Thermostatenblock nur noch etwa 0·p1 °C betragen. Für genaue Messungen muß aber die Temperatur noch um etwa eine weitere Größenordnung konstant sein. Das wird durch eine zweite Feinregelung des Thermostaten erreicht[23], der auf eine um soviel höhere Temperatur eingestellt wird, daß seine Wärmeabgabe an den Ofen um eine Größenordnung höher ist als der Maximalaustausch von Kalorimeter und Thermostat. In dieser Weise kann nämlich auch die Rückwirkung des Kalorimeters auf den Thermostaten ausgeregelt werden, was nach allen anderen Verfahren nicht möglich ist. Ein weiterer Vorteil ist natürlich dadurch gegeben, daß die Feinregelung innerhalb einer Umgebung ziemlich konstanter Temperatur ($\pm$0,1 °C) arbeitet und die Regelstrecke im Vergleich zum äusseren Ofen eine wesentlich geringere Leistung L und kleinere Zeitkonstante aufweist; auch die Totzeit dürfte etwas geringer sein. Das Verfahren des Doppelthermostaten wurde inzwischen auch für Messungen von spezifischen Wärmen übernommen[46]. Das axiale Temperaturgefälle scheint die Messgenauigkeit nicht so stark zu beeinflussen, wahrscheinlich weil der größte Anteil des Wärmestromes radial abfließt. Aus diesem Grunde empfiehlt es sich auch[23], das Reaktionsgefäß auf einen Asbestring zu stellen, um einen im Vergleich zum Kalorimetermantel zu grossen und zudem schlecht reproduzierbaren Wärmeaustausch mit dem Boden des Kalorimeters zu unterbinden. Trotzdem sollten in Boden und Deckel des Thermostaten Heizwicklungen angebracht werden, die vom Thermostaten-Regler über zusätzliche Kontakte geschaltet und so eingestellt werden, daß das axiale Temperaturgefälle nicht höher als 0·01 °C ist, was am besten durch ein verschiebbares Thermoelement nachgeprüft wird. Bei höherem Aufwand könnten natürlich auch die Zusatzheizungen über besondere Regler auf konstante Temperatur von Boden und Deckel geregelt werden. Ob dieser höhere Aufwand zu einem entsprechenden Gewinn an Meßgenauigkeit führt, wurde jedoch noch nicht untersucht, weil bereits eine ausreichende Meßgenauigkeit erzielt worden war[23].

1.56. *Adiabatische Regelungen*

Die unter **1.54** und **1.55** zusammengefaßten Methoden sind nach eigenen Versuchen auch für adiabatische Reglungen bei Messungen von spezifischen Wärmen geeignet. Dazu wird das Kalorimeter mit einer elektronisch konstant gehaltenen Leistung L aufgeheizt, die Temperaturdifferenz $(T_k - T_t)$ durch Einstellung eines Kompensationsapparates entsprechend der in Vorversuchen ermittelten adiabatischen Bedingung vorgegeben, und die Abweichungen von diesem Sollwert dem Modulationsregler als Signal zugeführt. Ausserdem wird die Temperaturdifferenz zwischen Thermostat und Ofen auf einen zweiten Regler gegeben, der eine durch Vorversuche bestimmte günstige Temperaturdifferenz einstellt.

Mit höheren Temperaturen nimmt aber der Leistungsbedarf von Ofen und Thermostat schnell zu, so daß die steilen Modulationsregler sehr bald ausserhalb ihres Proportionalitätsbereichs geraten würden. Es sind daher für beide Regelstrecken Nachfahrvorrichtungen für die Regeltransformatoren erforderlich. Schon lange ist das Verfahren bekannt, den Stellmotor eines Regeltransformators ebenfalls über die Kontakte des Zweipunktreglers so zu steuern, daß bei Einschalten der höheren Leistung der Stellmotor den Regeltransformator nach höheren Spannungen verstellt, und umgekehrt. Dadurch wird offensichtlich erreicht, daß bei zu geringer Leistung der Thermostatenheizung über die dann zunehmenden Einschaltzeiten die Leistung durch Höherregelung der Spannung vermehrt wird. Diese Methode hat allerdings den Nachteil einer überflüssig grossen Beanspruchung des Stellgliedes. Es läßt sich ausserdem nicht immer mit einfachen Mitteln erreichen, daß der Stellmotor in beiden Richtungen dieselbe Drehzahl aufweist, was implizit vorausgesetzt wird.

Es ist daher besser[11], mit zwei summierenden Kippkreisen die Aus- und Einschaltzeiten zu vergleichen und erst dann den Stellmotor in einer der beiden Richtungen laufen zu lassen, wenn das Verhältnis beider Zeiten einen bestimmten Erfahrungswert überschritten hat.

Bei Anwendung der unter **1.54** bis **1.56** beschriebenen Verfahren darf natürlich niemals übersehen werden, daß primär die E.M.K. eines Thermoelements auf einen konstanten Wert geregelt wird, und eine entsprechend genaue Regelung der Temperatur nur dann zustande kommt, wenn die E.M.K. für die Temperatur auch mit dieser Genauigkeit repräsentativ ist. Erfahrungsgemäß wird aber die Messgenauigkeit von Reaktionskalorimetern durch langsame und stetige Verschiebungen der Temperatur, etwa durch Alterung der Thermoelemente, nicht nennenswert beeinflußt. Sogar eine allmähliche Änderung des Kompensationsstromes, die einer Temperaturänderung von einigen hundertstel Grad in 24 Stunden entsprechen würde, ist harmlos; es ist sogar besser, den Kompensationsstrom während einer Messung nicht nachzustellen. Gegebenenfalls lassen sich Änderungen der absoluten Temperatur als Korrektur in Gl. (1) einführen.

2. SPEZIELLER TEIL

2.1. Messungen von Bildungswärmen

Bestimmungen von Mischungswärmen flüssiger Metalle werden durch einfache Vereinigung beider Partner im Reaktionsgefäß ausgeführt[39, 42, 47–54]. Bildungswärmen fester Legierungen können ebenfalls durch direkte Synthese bestimmt werden, wenn die Komponenten pulverförmig vermischt und in das Kalorimeter eingeworfen werden[55–58]. Dadurch wird allerdings eine gewisse Unsicherheit im Wärmeinhalt der Probe und durch den schwer erfassbaren Wärmeaustausch beim Einwurf eingeführt. Das Verfahren beschränkt sich ausserdem auf Reaktionen, die bei der fraglichen Temperatur schnell und vollständig verlaufen. Allgemeiner anwendbar ist die Methode der Lösungskalorimetrie in flüssigen Metallen[59–71]. Dabei treten die gleichen Schwierigkeiten auf wie bei Zimmertemperatur: es muß ein flüssiges Metall gefunden werden, in dem beide Randkompo-

nenten und alle intermediären Phasen sich schnell und vollständig lösen, und die Bildungswärme wird als Differenz der Lösungswärmen der betreffenden Phase und der unverbundenen Randkomponenten gefunden. Aluminiumlegierungen lassen sich bis herab zu etwa 300°C in Zink- oder Zink–Zinnmischungen lösen[69–71]. In dieser Weise können noch sehr geringe Bildungswärmen von *ca.* 1 kJ/g-At und ihre Aenderungen mit der Konzentration von einigen 100 J/g-At in befriedigender Weise bestimmt werden.

Von Interesse ist ein weiteres Verfahren der direkten Synthese durch adiabatisches Aufheizen der unverbundenen Randkomponenten bis zum vollständigen Ablauf der Reaktion, wobei sich die Bildungswärme als Differenz gegen die besonders bestimmten spezifischen Wärmen ergibt. Diese Methode wurde mit einer einfachen Apparatur bei einer Genauigkeit von etwa 10 Prozent angewendet[72]; mit präzisen Apparaturen läßt sich die Messung wahrscheinlich auf eine Genauigkeit von 1 Prozent verbessern. Erfahrungen über Messung von Reaktionswärmen an anorganischen und organischen Substanzen bestehen bereits[5, 12–21], und über kalorimetrische Messungen der Verformungsenergie von Metallen, u.a. durch Lösungskalorimetrie in flüssigem Zinn, liegt ein zusammenfassender Bericht vor[73].

2.2. Messungen von spezifischen Wärmen und Umwandlungswärmen

Bei diesen Verfahren gibt es zwei verschiedene Möglichkeiten, das Kalorimeter zu gestalten. Bei Festkörpern mit geringem Dampfdruck läßt sich nämlich schon allein die Probe durch Anbringung einer Heizwendel und der notwendigen Thermoelemente zu einem Kalorimeter ausbilden[74]. Vorteilhaft ist dabei der einfache Aufbau und der direkte Wärmeübergang von der Heizwendel auf die Probe. Von Nachteil ist dagegen die (u.U. aber nur geringe) Unsicherheit der spezifischen Wärme der keramischen Teile und Drähte, die nicht durch einen Leerversuch bestimmt werden kann. In allen anderen Fällen arbeitet man mit einem besonderen Kalorimeter, das die Heizwicklungen und Thermoelemente enthält und dessen Wasserwert $W(T)$ durch eine Meßreihe mit dem leeren Kalorimeter genau bestimmt werden kann. Ein weiterer Vorteil besteht in der Möglichkeit, die Proben schnell wechseln zu können. Nachteilig kann sich die thermische Verzögerung und mögliche Überhitzung des Kalorimeters bei hohen Leistungen auswirken. Differentialkalorimeter[75] haben den zusätzlichen Nachteil, daß die $K(T)$-Werte von der Beschaffenheit der Oberfläche abhängen und ihr Unterschied nicht ohen weiteres bestimmt werden kann. Bei Relativmessungen wurde der Versuch gemacht[76], diese Schwierigkeit durch bessere Wärmeleitung unter Verwendung von Wasserstoff als Füllgas zu umgehen. Bei Substanzen schlechter Wärme- und Temperaturleitfähigkeit können die thermischen Verzögerungen Schwierigkeiten bereiten. Durch Füllung solcher Substanzen in viele Bohrungen eines Aluminiumblocks liess sich jedoch bis 500°C eine Genauigkeit von 0·1 Prozent erzielen[77]; bemerkenswerterweise wird die Aufheizung öfters unterbrochen, um aus dem Gang der Vorund Nachperiode die Abweichungen vom adiabatischen Verhalten zu ermitteln.

2.3. Spezielle Verfahren

Es bleiben noch die Methoden zu erwähnen, bei denen bei intermetallischen Phasen durch Abschrecken von höheren Temperaturen ein metastabiles Gleichgewicht eingefroren und anschließend durch kontinuierliches oder plötzliches Aufheizen auf eine bestimmte Temperatur nicht nur die Wärmetönung, sondern auch die Kinetik des Über ganges in das Gleichgewicht verfolgt wird. Bei kontinuierlichem Aufheizen ergeben sich die Umwandlungswärmen wieder als Differenzen gegen die spezifischen Wärmen[78–79], während bei plötzlicher Erwärmung auf eine konstante Versuchstemperatur die kalorischen Effekte nach der Wärmeströmungsmethode bestimmt werden[80–89].

Ein sehr summarisches Verfahren zur Bestimmung von spezifischen Wärmen ist die Drahtmethode, bei der die Probe mit kurzen Impulsen auf hohe Temperatur aufgeheizt wird und sich anschließend wieder rasch auf Zimmertemperatur abkühlt. Diese älteren[90] und neueren Methoden[91] zählen eigentlich nicht mehr zur Kalorimetrie bei höheren Temperaturen, weil nur die Probe auf hohe Temperaturen gebracht wird.

3. ENTWICKLUNG UND HEUTIGER STANDARD DER MESSMETHODIK

An der Perfektion der Kalorimetrie bei tiefen Temperaturen und bei Zimmertemperatur sollte nicht übersehen werden, daß diese Verfahren in längeren Zeiträumen auf Grund der Erfahrungen aus sehr vielen Arbeiten entwickelt wurden. Die Zahl der Untersuchungen mit H.T.K. ist dagegen vergleichsweise noch gering. Hinreichende Kenntnisse über den zweckmäßigen Aufbau zuverlässiger Reaktionskalorimeter wurden erst in den letzten Jahren erarbeitet, so daß die Summe der vorliegenden Erfahrungen sich zwar, vor allem in letzter Zeit, erfreulich vermehrt hat, aber noch keineswegs als ausreichend angesehen werden sollte. Die Entwicklung der H.T.K. nach noch höheren Temperaturen, nach besserer absoluter und relativer Genauigkeit und nach möglichst einfachen, zweckmässigen, betriebssicheren und leistungsfähigen Anordnungen ist daher noch immer Gegenstand der Forschung, umsomehr als die Arbeiten der letzten Jahre eindeutig gezeigt haben, daß durch entsprechende Fortschritte Forschungsbereiche zugänglich gemacht werden, die nach älteren Verfahren nicht in befriedigender Weise untersucht werden konnten, wie beispielsweise die systematische Erforschung der Bildungswärmen in metallischen Systemen.

Die Entwicklung der H.T.K. ist eine Frage der Beherrschung der Reproduzierbarkeit der Temperaturänderungen in Thermostat und Kalorimeter und ihrer genauen Messung. Fortschritte lassen sich an der Zuverlässigkeit der elektrischen Eichung beurteilen, die daher ein wesentliches Kriterium der Güte eines Kalorimeters darstellt. Sie wurde schon vor etwa 20 Jahren bei Messungen der spezifischen Wärmen[28, 75] und der Schmelzwärmen[31–33] eingeführt, konnte aber erst in letzter Zeit bei H.T.K. für Reaktionswärmen angewendet werden[23, 42].

Der heutige Standard der Messungen von Reaktionswärmen ist durch folgende Merkmale gegeben.

(a) Nach dem Verfahren der Erwärmungskalorimetrie können bei Temperaturen bis 1000°C Wasserwerte durch elektrische Eichung mit einem mittleren Fehler der Einzelmessung von 0·5–2 Prozent, je nach Temperaturbereich und Größe der Wärmemenge, bestimmt werden, invariant gegenüber Variationen der Versuchsdauer und der Wärmemenge.

(b) Ergebnisse verschiedener Autoren mit elektrisch geeichten Kalorimetern stimmen in der Regel innerhalb von 1–2 Prozent überein; etwaige größere Diskrepanzen mögen eher durch chemische als durch apparative Fehlerquellen bedingt sein.

(c) Die Apparaturen können von in 1 bis 2 Wochen angelernten Beobachtern leicht und sicher bedient werden; Fehlmessungen durch Bedienungsfehler treten praktisch nicht auf. Automatische Regelungen gestatten dem Beobachter die Konzentration auf die eigentliche Messung; je nach Arbeitszeit können 2 bis 4 Messungen täglich ausgeführt werden. Reparaturen sind selten und werden in der Regel frühestens nach einem Jahr ununterbrochener Betriebszeit fällig; die Apparaturen können verhältnismäßig leicht ausgebaut werden, so daß auch größere Reparaturen an Heizwicklungen und Thermoelementen in wenigen Tagen ausgeführt werden können. Alle Stromzuführungen werden von unten in die Apparatur eingeleitet, so daß die Manipulation von Proben ungestört von oben erfolgt, und Thermoelemente können zwecks Reparatur oder Nacheichung aus der laufenden Apparatur entnommen werden.

(d) Kriechströme treten bei Temperaturen bis 1000°C nicht auf. Aus- oder Einschalten eines beliebigen Stromkreises beeinflußt andere Messkreise schlimmstenfalls durch einen kurzen induktiven Stromstoß.

Bei der Messung von wahren spezifischen Wärmen und Umwandlungswärmen wurde bis heute folgender Stand erreicht:

(a) Ausdehnung des Temperaturbereichs bei adiabatischer Aufheizung bis 1600°C, bei der Erwärmungsmethode bis 1300°C;
(b) eine absolute Genauigkeit von 0·1 Prozent bei adiabatischer Aufheizung, bis 500°C auch bei Substanzen schlechter Wärmeleitfähigkeit;
(c) Entlastung des Beobachters durch partielle oder vollständige automatische Reglung des Kalorimeters einschließlich des Meßvorganges.

Im übrigen gelten die bei den Reaktionskalorimetern aufgezählten Merkmale. Die Versuchsdauer kann natürlich sehr lange sein, wenn ein größerer Temperaturbereich durch adiabatisches Aufheizen durchlaufen werden muß, weil geringe Aufheizungsgeschwindigkeiten von *ca.* 1°C/min erforderlich sind. Dieser Umstand fördert die Entwicklung vollautomatischer Kalorimeter. Die Frage der Zuverlässigkeit der adiabatischen Regelung und der Sicherheit der nach dieser Methode gewonnenen Absolutwerte bedarf einer aufmerksamen, kritischen Prüfung, wenn absolute Genauigkeiten von besser als 1–2 Prozent angestrebt werden.

Diese Ausführungen mögen die experimentellen Möglichkeiten der Hochtemperaturkalorimetrie, ihre prinzipiellen Schwierigkeiten und deren weitgehende Überwindung durch neue Konstruktionen und Regelverfahren gezeigt haben. Aus den Arbeiten und Erfahrungen vieler Forscher hat

sich so in den letzten 25 Jahren eine brauchbare experimentelle Methodik der kalorimetrischen Messungen bei höheren Temperaturen herausgebildet, die zu interessanten Anwendungen geführt hat, wie sich an der erfreulichen Zunahme von Arbeiten aus diesem Gebiet in den letzten Jahren erkennen läßt. Es sind daher noch weitere wesentliche Fortschritte zu erwarten.

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VOL.
2
1961

DISCUSSION ON DOCUMENTATION OF THERMOCHEMICAL DATA

H. F. Stimson (*U.S.A.*): Computations of values of thermodynamic properties are based upon the thermodynamic temperature scale. With the trend towards increased accuracy in calorimetric measurements a more exact knowledge of the thermodynamic scale is desirable. Needless to say, we would like to know the true thermodynamic temperature scale, but lacking this we use the International Scale. For thermodynamic computations the difference between scales is not yet of great importance; below the sulphur point the greatest reported difference between the scales is less than one part in 4000 of the temperature. Corrections could be made for such differences.

The International Scale, on the other hand, makes it possible to realize temperatures much more precisely and reproducibly. The definition of the International Scale can be and is being improved from time to time to make the scale more precise and reproducible without changing values on this scale by more than the experimental error of measurement. Except for temperatures above the gold point, values of temperature on this scale have remained essentially the same since 1927.

Eventually the present International Scale will be changed to one that is more closely thermodynamic. If we were to change the values of temperature on the International Scale in the present state of our knowledge, the question is, would the change be worthwhile? Frequent changes lead to more confusion than they correct. My recommendation is for more researches done with meticulous care so that systematic errors will be removed. When our accuracy is thus increased several fold over that which we have at present, then a new scale can be adopted that will definitely be more closely thermodynamic than the present International Temperature Scale.

In summary, more accurate data are needed over the entire range of the practical scale. Let us not change the values of temperature on the practical scale, however, until we can be sure the new practical scale is considerably closer to the thermodynamic. If this change is made too soon an excessive amount of confusion may result.

K. S. Pitzer (*U.S.A.*): First, I would like to state my agreement with Dr Stimson in his argument against frequent changes in the temperature scale adopted by the standardizing laboratories. Frequent changes cause great confusion in later years; it is much better to make major improvements in the scale at infrequent intervals.

Secondly, I would like to suggest and hope that we may soon abandon the use of arbitrary and somewhat non-thermodynamic temperature scales just as the use of international electrical units was abandoned ten or fifteen years ago. With the new definition of the Kelvin scale in terms of the single fixed point at the triple point of water, we should be able to determine the thermodynamic scale to an accuracy as high as the present reproducibility

of working thermometers. Then there would be no need to define an arbitrary scale such as the present International Scale. Instead, the standardizing laboratories could calibrate working thermometers on the thermodynamic, Kelvin, scale to the full accuracy to which the thermometer was expected to reproduce its behaviour.

I realize that there are many difficulties to be overcome before such a change is possible, and I do not pretend to see how best to overcome these obstacles. I just want to emphasize that we here at this meeting and, in my opinion, most of those who need precise temperature measurements are dealing with thermodynamic temperature. Thus any new working temperature scale should certainly agree completely with the knowledge of the thermodynamic scale at the time of adoption. Also one would hope that the present uncertainties in the thermodynamic scale, which have been referred to today, will be removed soon.

H. Moser (*Deutschland*): Wie ich in meinem Vortrag erwähnt habe, stimmen die Messungen verschiedener Autoren über die Abweichungen zwischen der thermodynamischen und der Internationalen Temperaturskala noch nicht so gut überein, um jetzt schon eine Angleichung der zweiten Skala an die erste zu ermöglichen. Es sind jedoch bereits Messungen in weiteren Staatslaboratorien über dasselbe Problem im Gange, die voraussichtlich in einigen Jahren abgeschlossen sein dürften. Erst dann wird man entscheiden können, ob eine Änderung der internationalen Skala zweckmäßig und sinnvoll ist.

Es wird auf lange Zeit nicht möglich sein, die Genauigkeit thermodynamischer Temperaturmessungen so zu steigern, daß sie mit der Reproduzierbarkeit eines Gebrauchsthermometers (wie z.B. des Platinwiderstandsthermometers) vergleichbar ist. Da gasthermometrische Messungen außerdem viel schwieriger durchführbar sind als diejenigen nach den Verfahren der jetzigen Internationalen Temperaturskala, wird man auf diese nicht verzichten können. Eine andere Bezeichnung für diese konventionelle Skala, etwa der Name "Praktische Internationale Temperaturskala" erscheint zweckmäßig. Entsprechende Vorschläge sind bereits gemacht.

VOL. 2 1961

IRREVERSIBLE THERMODYNAMICS

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There are alternative sets of postulates which yield entirely equivalent results for several important theories. In such cases the choice of a particular set of postulates may be based upon mathematical simplicity, close relationship to experiments or to the nature of the theory, or merely personal taste. While the postulate of conservation of energy is usually presented in similar form for thermodynamics or statistical mechanics, the form of the postulate comprising the second law is commonly very different. In thermodynamics the postulate may be in terms of the impossibility of an isothermal engine producing work at the expense of heat while in quantum statistical mechanics one postulates equal *a priori* probability for all individual quantum states. It is the purpose of the present paper to point out that there are such alternatives for the additional postulate necessary to derive the Onsager equations for the irreversible thermodynamics of processes in the linear rate law region near equilibrium.

The heat engine, which was the primary subject of interest during the original development of classical thermodynamics, comprises both reversible and irreversible processes. In such machines the separation of the reversible changes of the working fluid from the frictional effects and the irreversible heat leaks is practically self-evident. Thus in his classic paper "On the dynamical theory of heat", Kelvin[1] assumes this separation of processes to be obvious in ordinary heat engines where he simply specifies "perfect engine", but he discusses the separation at length for thermoelectric phenomena as a separate postulate.

The magnificient work of Gibbs, van't Hoff, and others, showing the applicability of thermodynamics to physicochemical equilibria distracted attention for a time from steady-state problems. But in 1926 Eastman[2] applied Kelvin's method to thermo-osmosis, the Soret effect, and the properties of thermocells. Wagner[3] and London[4] used similar methods soon thereafter. In these treatments it is assumed that the irreversible heat flow constitutes a process which is independent of the processes transferring the material components. Then the second law of thermodynamics requires the entropy to be a maximum with respect to any transfer of matter and thus determines the steady-state distribution.

The new formulation of the near-equilibrium problems in 1931 by Onsager[5] in terms of linear rate laws and his derivation of the reciprocal relationships gave new impetus to theoretical work and de Groot[6], Prigogine[7] and others soon applied this new formulation to a wide variety of phenomena. It was implied in some of these treatments that the new methods were more rigorous in spite of the fact that in so far as the problems had been treated previously by Kelvin's methods, the results were identical. However, the

new formulation is more convenient in many instances. Onsager's derivation of his reciprocal relationships is based upon the postulate of microscopic reversibility and upon statistical arguments concerning the decay of fluctuations. Among the several other statistical derivations which have been given is that by Parlin, Marcus and Eyring[8] in terms of absolute reaction rate theory.

While the convenience and power of the Onsager formulation is a great advantage, this may be attained from the Kelvin postulate of independent processes, as has been demonstrated by Li[9]. Indeed, the present author believes that this form of the basic postulate is most appropriate to thermodynamics as well as having a historical precedent. A simple derivation of the Onsager relationships from the Kelvin postulate is given below. This presentation is essentially similar to that of Li but is more concise and avoids one possibly misleading implication*.

Following the usual definitions, one selects co-ordinates a_i which measure the amounts of various components of matter, of heat, *etc.*, transferred from one portion of the system to another. The zeros of these co-ordinates are selected at the state of equilibrium. Hence the entropy change from equilibrium, to the second order, is

$$\Delta S = -\tfrac{1}{2} \sum_{i,j} g_{ij} a_i a_j \tag{1}$$

The rate of change of a co-ordinate, $\dot{a}_i$ is a flux which is commonly given the symbol $\mathcal{J}_i$. Also the restoring force or potential difference associated with the i-th co-ordinate is defined by the equation

$$X_i = \frac{\partial(\Delta S)}{\partial a_i} = -\sum_j g_{ij} a_j \tag{2}$$

The rate of increase of entropy, within the region of validity of equation (1), is

$$\dot{S} = -\sum_{i,j} g_{ij} \dot{a}_i a_j = \sum_i \mathcal{J}_i X_i \tag{3}$$

where we note the particularly simple form of the expression as a sum of terms $\mathcal{J}_i X_i$.

In practice it is usually easier to write an expression for the rate of entropy increase directly in terms of defined fluxes and differences of temperature, pressure, concentration, *etc.*, within the system. Then the potential conjugate to a given flux may be found by identifying the complete factor which, multiplied by $\mathcal{J}_i$, constitutes a term in the equation for $\dot{S}$.

* It should be noted that there is no limit upon the number of independent microscopic processes. For example in a thermo-osmosis system there might be several different membranes and each would have its characteristic heat of transfer for passage of matter. However, the number of fluxes required to describe the macroscopic system is fixed by the number of components, *etc.* While Li's resultis identical with that given here, his use of a square transformation matrix implies an unnecessary limitation of equal numbers of fluxes in the two sets.

VOL. 2 1961

At equilibrium all gradients X_i are zero and by thermodynamics all fluxes must be zero. Also for systems not at equilibrium $\dot{S}$ must be positive regardless of the signs of the X_i. Consequently the $\mathcal{J}_i$ must change sign with the X_i and one expects a linear dependence of $\mathcal{J}_i$ on X_i to be a good approximation for small X_i.

An arbitrary selection of fluxes cannot be expected to yield those microscopic processes which are actually independent of one another but *we postulate that such non-interacting processes exist in the region of first-order rate laws.* For this special set of fluxes, $\mathcal{J}_j'$, each flux depends only upon its corresponding potential gradient X_j', hence

$$\mathcal{J}_j' = L_j' X_j' \tag{4}$$

where L_j' is the linear rate constant.

The arbitrary fluxes $\mathcal{J}_i$ can be expressed in terms of the non-interacting fluxes $\mathcal{J}_j'$ by a linear transformation

$$\mathcal{J}_i = \sum_j \alpha_{ij} \mathcal{J}_j' \tag{5}$$

and this transformation may be substituted into equation (3) for entropy production

$$\dot{S} = \sum_j \sum_k \alpha_{ij} \mathcal{J}_j' X_i \tag{6}$$

The coefficient of $\mathcal{J}_j'$ in equation (6) is

$$X_j' = \sum_i \alpha_{ij} X_i \tag{7}$$

Substitution of these results and the rate equations (4) for the independent processes into equations (5) yields

$$\mathcal{J}_i = \sum_j \sum_k \alpha_{ij} L_j' \alpha_{kj} X_k \tag{8}$$

and if we define a new rate constant L_{ik}:

$$\mathcal{J}_i = \sum_k L_{ik} X_k \tag{9}$$

$$L_{ik} = \sum_j \alpha_{ij} \alpha_{kj} L_j' \tag{10}$$

But it is evident from equation (10) that

$$L_{ik} = L_{ki} \tag{11}$$

which, for various i, k, constitute the Onsager reciprocal relationships.

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VOL.
2
1961

TRANSITIONS AND THERMAL ANOMALIES IN SILVER OXIDE

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In 1937 Pitzer and Smith[1] measured the heat capacity of silver oxide (Ag_2O) over the range 13–300°K and found anomalously high values in the range 20–40°K. Hysteresis effects were noted with respect to the excess heat capacity. The entropy associated with the anomaly was approximately 0·5 cal $°C^{-1}$ $mole^{-1}$. Kobayashi[2] measured the heat capacity of silver oxide at higher temperatures and observed a heat evolution of approximately 315 cal/mole in the range 100–200°C the first time that a given sample was heated through this region. Repeat heating gave no further heat evolution. In each case the sample was precipitated from aqueous solution and was dried at temperatures not exceeding 115°C. The present investigation was designed to yield further information about these peculiar effects.

EXPERIMENTAL

Samples

Several silver oxide samples were prepared under a variety of conditions. The decomposition pressure of silver oxide reaches 1 atm at about 460°K, hence high temperature preparations had to be carried out in a bomb under oxygen pressure. A platinum lining was used in the bomb. In all cases the samples were initially precipitated from aqueous solution at room temperature in the absence of carbon dioxide. Care was taken to avoid contact with reducing agents. Analyses yielded the theoretical compositon Ag_2O within experimental error. No reduction such as that reported by Faivre[3] was observed. Spectroscopic analysis showed 0·05 per cent of Cu and less than 0·01 per cent of other impurities. The samples may be placed in three classes: (A), precipitated and dried at 95°C; (B) precipitated, dried, and annealed by heating to 180°C under 140 atm pressure of oxygen; and (C), precipitated, crystal growth promoted under 200 atm of oxygen in contact with water for 20 days at 325°C, and then dried in pure oxygen at 110°C.

Optical microscopy showed material (A) to be exceedingly fine whereas material (C) had crystals of approximately 0·02 mm edge length. X-ray diffraction showed a lattice parameter of 4·72 $\pm$ 0·01 Å for all samples, but samples (B) and (C) showed somewhat sharper lines. Electron spin resonance measurements gave no evidence for unpaired electrons in either annealed or unannealed samples.

Thermal measurements at 20–40°K

The low temperature heat capacity measurements were made in the usual manner. Minor variations in the calorimeter will be described when the measurements are presented in detail. *Figure 1* shows as open circles and

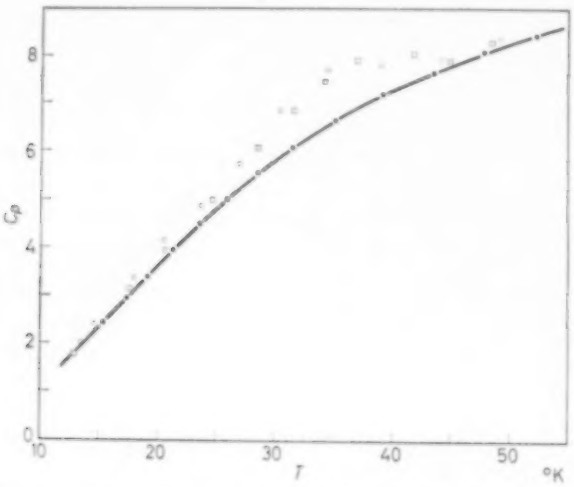

Figure 1. The heat capacity of silver oxide. ○, □ results of Pitzer and Smith[1] on two different samples of type (A); ● new results on large crystals (sample C)

squares two of the series of measurements of Pitzer and Smith on a sample of type (A) and as closed circles the new measurements on sample (C), i.e. large annealed crystals. It is apparent that the anomaly has disappeared. The large crystals show slightly smaller heat capacity over the remainder of the temperature range. This effect of surface or of particle size has been observed for other substances.

Heat capacity measurements have also been made on samples (B) but calculations are not yet complete. The anomaly is still present but is substantially reduced in magnitude as compared with sample (A). The entropy value calculated for sample (C) is given in *Table 1* along with the values for sample (A) and that reported by Hamer and Craig[4] from cell measurements. The value for the large crystals of sample (C) is in excellent agreement with that of Hamer and Craig.

Table 1. The entropy of silver oxide at 298·15°K (cal °C^{-1} mole^{-1})

Sample A	total	29·09
	without hump	28·61
Sample C		28·38
Hamer and Craig[4] (cell E.M.F.)		28·32

Thermal measurements at 370–470°K

The apparatus used in this range was of the differential thermal analysis type described by Pask and Warner[5]. We are indebted to Professor Pask

VOL. 2 1961

for the use of this equipment. The apparatus is sensitive to heat effects of 0·2 to 0·5 cal with a sample of 2 g of silver oxide. Heating curves for unannealed samples of type (A) uniformly showed exothermic peaks near 200°C in agreement with the result of Kobayashi. Neither the annealed samples (B) and (C) nor samples of type (A) which had been heated through the 200°C peak showed any exothermic peak. All samples absorbed heat in the region above 250°C; this was presumably caused by decomposition of silver oxide to metal and oxygen.

DISCUSSION

The measurements reported above show that neither of the thermal anomalies observed for freshly precipitated and dried silver oxide is observed with large perfect crystals. Both anomalies are associated in some way with the large surface or the crystal imperfection of the precipitated material. The heat evolution above room temperature could readily arise from the annealing of crystal defects and the reduction of surface by crystal growth. We have observed similar effects in magnesium oxide. Since the energies associated with defects or surface may be large and it is known that the precipitated material is extremely finely divided, there is no contradiction with the rather substantial heat of 315 cal/mole observed by Kobayashi[2].

It is much more difficult to explain the low temperature anomaly. Since the effects at 20–40°K are reversible, although with hysteresis, only thermal energies corresponding to these temperatures can be involved. Thus the appropriate quantity for interpretation is the entropy of approximately 0·5 cal $°C^{-1}$ $mole^{-1}$. If the surface atoms were shifting from single positions to random distributions over a modest number of positions, then roughly 10 per cent of the atoms would have to be on the surface. This seems unlikely. Another possibility is some sort of condensation or aggregation, whereby the entropy change per mole of surface atoms might be 10–20 cal $°C^{-1}$ $mole^{-1}$. Even this postulate requires 1 to 5 per cent of the atoms to participate, which seems a large percentage.

It is known from work[6] on magnesium oxide that surface entropy of very fine material can approach 0·25 cal $°C^{-1}$ $g\text{-}atom^{-1}$, but in that case the extra heat capacity is distributed more uniformly over the entire temperature range. The values in *Table 1* for sample (A) (without hump) and for sample (C) show that this difference is present in the silver oxide in addition to the anomaly at 20–40°K.

The crystal structure of silver oxide has an unusual characteristic which might lead to abnormal behaviour. The silver oxide structure comprises two separate but interpenetrating lattices which are nowhere directly bonded to one another. Thermal energy at high temperatures would cause each lattice to occupy on the average the centre of the vacancies of the other lattice and thereby have maximum freedom for thermal motion. Conceivably, however, at low temperatures the two sub-lattices could move toward one another and find a lower potential energy in an unsymmetrical state. Since this would involve co-ordinated motion of all atoms of a given crystal, it is possible that the rate of transformation is significant only for very small crystals. If this sort of change is involved, the restraining forces for lattice vibrations should be somewhat larger in the low temperature

asymmetric form. From the points in *Figure 1* it appears that the heat capacity curves cross at about 14°K with the small crystals showing smaller heat capacity below that temperature. This result is consistent with the postulated type of change, but the accuracy of the measurements below 20°K is hardly great enough to make this conclusion completely definite. Various aspects of this problem are under further study.

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VOL.
2
1961

SOME THEORETICAL ASPECTS OF PHASE TRANSITIONS

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Thermodynamics alone puts but few limitations on the nature of phase transitions. Coupled, however, with a statistical mechanical interpretation, it provides occasionally some insight into this nature.

Consider the usual simple proof that the Helmholtz free energy, $A(V,T)$ can never have a region in which the plot against V at constant T is concave downward, i.e. for which $(\partial^2 A/\partial V^2)_T < 0$. Suppose there were such a region, *Figure 1*. We draw the straight line tangent at V_1 and at $V_2 > V_1$. Consider a system of volume V $(V_1 < V < V_2)$ then a distribution with

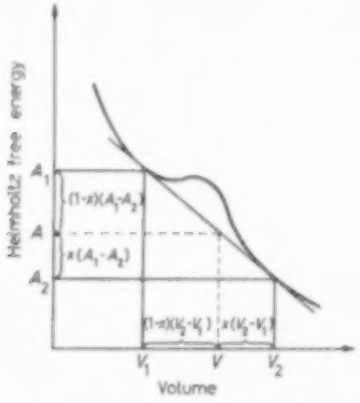

Figure 1

weight fraction $x = (V_2 - V)/V_2 - V_1)$ occupying the volume xV_1 and with fraction $(1 - x) = (V - V_1)/(V_2 - V_1)$ occupying the volume $(1 - x)V_2$ will have total volume V. Provided the system is so large that the interfacial free energy can be neglected, the total free energy will be $A = xA_1 + (1 - x)A_2$, namely it will lie on the straight line between the two volumes V_1 and V_2. But since the equilibrium condition at fixed V and T is that A be a minimum, the two-phase system will be the equilibrium state for all volumes between V_1 and V_2.

Since $P = -(\partial A/\partial V)_T$ is constant along the line, the two-phase region has a constant pressure. For the sketch shown, since $(\partial^2 A/\partial V^2)_T > 0$ at both V_1 and V_2, the compressibilities, $K = -V(\partial V/\partial P)_T = V/(\partial A^2/\partial V^2)_T$ approach finite values at the phase transition.

The argument is conclusive for thermodynamic equilibrium. However, the inverse conclusion, which is sometimes drawn, that if there is a phase transition there must exist some uniquely defined continuous $A(V,T)$ curve above the straight portion, is unjustified. This conclusion is sometimes extrapolated from the remarkable success of the simple van der Waals equation which shows the familiar P–V loop in the condensation region, corresponding to just such a continuous A–V curve with A concave downward. The conclusion is further substantiated by the fact that in many, if not all, cases the metastable region can be traced experimentally beyond the transition volumes. However, these metastable curves are never followed into the region where A is concave downward, $(\partial P/\partial V)_T > 0$.

It is my opinion that no such continuous A–V curve has any unique meaning. The usual description is that such a continuous A–V curve is that which would obtain if the system were constrained to a uniform density. However, the problem arises as to how uniform is uniform. If $(\partial^2 A/\partial V^2)_T < 0$ fluctuations of any kind in the density lead to a more stable configuration, and since positive surface free energies are meaningless between regions differing in a continuous parameter for infinitesimal differences in that parameter, the fluctuations on a molecular level will be stable. In short, even if the system is constrained to a lattice with one molecule per site, the equilibrium configuration will have the molecules at the cell corners with as many clustered together as the assumed lattice allows. The value of A will depend on the lattice structure assumed and will be utterly different if a lattice permitting two or more molecules per cell is considered.

An interesting example of a phase transition in which the metastable curves for the two phases can be traced to overlapping volumes is that of some experiments made by the use of electronic computers on hard sphere molecules. These have been made by Alder and Wainwright in Livermore and by Wood in Los Alamos, the latter following a method first used by Metropolis, Rosenbluth, Rosenbluth, Teller and Teller.

The computers treat an infinite system of hard spheres, the initial positions and velocities of which are exactly periodic in cubic cells containing n molecules, so that for all future time the system is constrained to have no density fluctuations nor energy fluctuations in any volume containing exactly an integral number of these cubic cells. In different experiments the number n is chosen as 4, 8, 16, 32, . . . 512, the latter being the largest number treated. The results are essentially independent of n for $n \geqslant 32$. Alder and Wainwright ask the computer to tell them the positions and velocities after time t by actually computing the results of all collisions. Wood uses the $M\,R^2\,T^2$ method, by which random displacements with the appropriate weighting are made. The number of random moves in this case plays a similar role to the time t in the other computation. In both cases the pressure P is computed from the pair distribution in space, and the results of the two methods are essentially identical.

At sufficiently large volumes the P–V curve is quite normal. At volumes considerably larger than close packing a strange phenomenon occurs. For the order of 10^5 moves or more the computed P shows the normal small fluctuation around some average value, $P_{\text{cr}}(V)$, but then suddenly jumps to a

VOL
2
1961

larger value, and fluctuates around the new average of $P_g(V)$ for another 10^5 or more moves. In at least one case a return to P_{cr} was observed. The spatial distribution that leads to P_{cr} is that of small displacements from the arrangement of a close-packed lattice, and few if any exchanges of the positions of the molecules occur. (Since the initial positions chosen are those of a close-packed lattice the " phase " with P_{cr} always appears initially.) If V is sufficiently large the distribution goes over in a few moves (that is in some 10^3 moves) to the distribution corresponding to $P_g(V)$.

Unfortunately, the free energy $A_{cr}(V)$ of the " phase " for which the pressure is $P_{cr}(V)$ cannot be obtained. That of the other " phase " is obtained from the $P_g(V)dV$ integral to the perfect gas limit where the integration constant is known. The function $A_{cr}(V)$ is left with an unknown integration constant, and the " equilibrium " pressure at which the transition occurs is unknown. However, since the negative slope

$$-(\partial A_g/\partial V)_T = P_g(V)$$

of the " gas phase " is much greater than that of the " crystalline phase " at low V values, it is clear that the two curves, A_g and A_{cr} must intersect, leaving a region concave downwards.

By an ingenious method Wood has "compressed" the metastable gas phase to low V values, and the distribution appears to go over into something resembling that of a body-centred cubic lattice.

Now it appears to me to be clear that the behaviour of this system shows that the " gas " or " fluid " phase has a positive surface free energy in contact with the " crystalline " phase.

In the discussion of the phase transition one proves that a transition occurs at equilibrium if the A–V curve is such that a tangent to it at two volumes V_1 and V_2 falls below the curve. However, the statement is only true if the surface free energy is neglected. This is always legitimate if the system is large enough, and under no constraint of uniform density. If, however, the surface free energy is positive, and a sufficiently large proportion of the system is at the interface, the argument would fail. The systems dealt with in these computer experiments are such that uniform density is maintained in cubic cells containing n molecules, and always $n < 10^3$. The system can become two-phase only by dividing every cell into the two phases. Counting that at least one molecular layer in each phase is at the interface, even for $n = 10^3$ one would have 200 molecules in each cell at an interface bisecting the cell, and another 200 at the interfaces with the adjacent cell. In all, about half the molecules would be at interfaces. If the surface free energy is positive it is clear why the system does not show the phase separation and the consequent volume range of constant P value. But unless the surface free energy were positive separation would occur. It seems evident that there are two distinct phases, crystalline and fluid, for these hard sphere molecules, and that the two phases have a positive surface free energy.

One might parenthetically remark that for this (classical) system the energy is purely kinetic and independent of volume. The whole dependence of A upon V lies in the entropy term, as does the surface free energy.

Could the calculations be carried out sufficiently long the relative entropies in the two phases could be evaluated by comparing the " times" spent in each phase. The transitions are so rare that this is impractical.

The foregoing discussion indicates that in the normal first-order transition the free energies of the two phases show a normal behaviour as the transition is approached. Abnormal increase in the compressibility or in the heat capacity is not to be expected. If such an abnormal " pre-transition " rise in either or both were observed it would indicate that the stable phase has, in its structure, some premonition of the approaching calamity. Such premonitory behaviour might be described as fluctuations in the stable phase, a, of groups of molecules into the arrangement of phase b. If $\Delta\mu$ is the difference, $\mu_b - \mu_a$, in the free energies per molecule for the two phases, the probability that a given set of n molecules would be in phase b would be $\exp - n(\mu_b - \mu_a)/kT$ were there no surface effects. The number on the interface is of order $n^{2/3}$, and if the interfacial free energy per (the area of one) molecule is σ then another factor of order $\exp - n^{2/3}\sigma/kT$ is introduced, which is the only remaining factor at the transition point for which $\mu_a = \mu_b$. We might decide that the new phase is unrecognizable unless it is at least the size of a cube with four molecules on the edge, having 8 molecules in the interior as the new phase, and the remaining $64 - 8 = 56$ molecules on the surface. The chance that a given set of 64 molecules is in such a fluctuation is then of the order $\exp - 56\sigma/kT$, which is hardly appreciable unless σ/kT is indeed very small. Using a rather small interfacial tension of 13 dyn/cm and an area of 10 Å^2 per molecule, $\sigma = 1{\cdot}3 \times 10^{-14}$ erg, σ/k is 100°K, so that σ/kT is of order $\frac{1}{3}$ at room temperature.

We may conclude that if two phases have a reasonable interfacial tension the fluctuations in either of the phases that presage the transition will be negligible. The situation is utterly different if the interfacial tension is extremely small, and were it, perchance, to become identically zero in value, we would expect a continuous rise of the heat capacity and of the compressibility to infinite values as the transition is approached.

The order of a phase transition is traditionally defined as that of the lowest derivative of the Gibbs free energy, G, which becomes discontinuous at the transition. First-order transitions are those for which there are non-zero first derivative discontinuities by the amounts ΔS and ΔV, whereas for second order transitions these are continuous but the next derivatives are discontinuous, so that C_p, K and β jump in value. The definition has the advantage of mathematical simplicity and apparent uniqueness, even if, on the one hand rather varied phenomena are classed as the same order, and on the other hand the order is not always easy to assign unambiguously from the experimental behaviour.

There exists an old objection to the possibility of existence of true second-order (or any even order) transitions. The objection is probably best answered by the apparent experimental existence of a considerable number of clear cases. However, it deserves mention with the probable theoretical answer.

The objection is that, on a G–T plot, the continuation of the curve for the phase of higher C_p, and therefore of greater concavity downward, lies at a lower free energy G than that of the phase which is observed to be

stable. The obvious answer is that the continuation does not exist. Physically, one assumes that there is some natural parameter which is a function of the state T and P, the change of which contributes terms to the heat capacity and compressibility, *etc.*, and which reaches some " dead-end stop " at the transition, so that beyond the transition it remains constant at this limiting value. Actually, as far as I know, all cases of second-order transitions for which there is a mechanistic physical explanation do have a natural parameter of this type. In the lambda transition of liquid helium the two-fluid model has this parameter as the fraction of superfluid, which reaches the natural limit of zero at the transition. Transitions explained by the onset of what one describes as free rotation have also such a parameter in the fraction of " freely rotating " molecules, which cannot exceed unity. In the case of superconductivity the parameter is the " energy gap " above the Fermi surface, which decreases to zero at the transition.

Unfortunately for so simple an explanation, any naïve interpretation of it would require the heat capacity to be completely normal on the side of the transition for which the parameter takes its constant limiting value. This is seldom the case, and in most experimentally known cases the heat capacity rises abnormally from both sides as the transition is approached.

Even the mathematical definition of a second-order transition runs into at least semantic difficulties when applied to the liquid helium case. The heat capacity rises logarithmically to infinity from both sides as the transition is approached. Since the rise is logarithmic the heat absorbed in the interval between $T_{tr} - \epsilon$ and $T_{tr} + \epsilon$ goes to zero as ϵ vanishes, so that the transition is not first order. In the sense that the two heat capacities at $T_{tr} - \epsilon$ and at $T_{tr} + \epsilon$ differ by a non-zero constant as ϵ decreases, there is a " jump " in the heat capacity, but at the transition it is between two infinite values.

There is one rigorous statistical mechanical statement that can be made linking the order of the transition and the distributions of molecules on the two sides of the transition. The statement is simplest in the classical case when the kinetic energy is always $(\frac{1}{2})kT$ per degree of freedom. The molecular distribution may be described by a hierarchy of probability density functions for increasing numbers, n, of molecules. The first of these $\rho_1(r)$ gives the probability density of finding a single molecule at r and the second, $\rho_2(r_1,r_2)$, is the probability density of finding simultaneously one molecule at r_1 and a second at r_2. In an nth order transition the probability density function, ρ_n, for n molecules is discontinuously different on the two sides of the transition, but the functions for fewer than n molecules remain continuous.

Finally I may mention one interpretation of what appears to be a second-order transition in some glasses, presented by Dr J. H. Gibbs at the Gordon Research Conference on Liquids in the summer of 1959. On cooling, most glasses show abnormally high heat capacities, and on " freezing " there is a sudden drop of the heat capacity. The entropy drops on cooling abnormally rapidly in the range of high heat capacity, then at a normal rate for lower temperatures, but usually stays well above the entropy of the crystalline material and approaches a positive non-zero value at absolute zero. The sudden change of heat capacity is primarily or solely due to the enormous

increase in viscosity and consequent almost zero rate of the internal reorientations toward the stable ordered structure.

However, some polymer glasses, the polymer of which can also be obtained as crystals, have a total decrease of entropy in this abnormal heat capacity range which takes them to essentially the same entropy as the crystal. Below the " transition " their heat capacities are closely the same as that of the crystal, and, if the crystal entropy is zero at absolute zero one concludes that the glasses approach (practically) zero entropy at absolute zero. If these facts are correct one must conclude that the " transition " occurs as the disorder entropy of the glass approaches zero.

In order to believe this at all one must remember that a vanishingly small entropy is still consistent with a considerable number of states in a macroscopic system. Since $S = k \ln \Omega$, a value of Ω, the number of microscopic states, as large as $10^{10^{20}}$ which is still a considerable number, would give an immeasurably small entropy in one mole of material.

Now Gibbs sets up the highly complicated expression, using the quasi-chemical approach, for the number of disordered complexions, Ω, as a function of the difference, ΔE, in energy between the glass and crystal, which in turn is determined by the number of " misplaced " links. The details of the calculation are quite complicated. However, the expression for $\ln \Omega$ extrapolates to zero, Ω to unity, at a value of ΔE greater than zero. In reality, of course, the approximate expression, which might be quite good for large ΔE fails at low values, where certain unique configurations corresponding to the partial crystalline order begin to have importance, and configurations for all $\Delta E > 0$ exist, indeed in great numbers, but not greater than, say, $10^{10^{20}}$. The glass system follows the approximate equation prediction fairly well for large Ω values, decreasing ΔE and Ω with lowering temperature, and finding it increasingly difficult to diffuse to the lower energy sites as Ω decreases and their number becomes smaller. This same decrease in sites available causes a rapid decrease in fluidity. By the time Ω had decreased to $10^{10^{20}}$ the molecules can no longer find the few peculiar configurations of really low energy, and the fluidity has sunk correspondingly. But by this time the configurational entropy has become immeasurably small.

Whether the picture indeed corresponds to reality I am not in a position to assert. In any case I find it plausible. The essential feature is that the low configurational entropy is adduced as a cause of the decrease in fluidity, the decrease in fluidity occurs at the same point as the true S *versus* ΔE curve changes character, and this occurs at an entropy so small as to be negligible.

VOL. 2 1961

TRANSITION TYPES IN HYDROCARBONS AND RELATED SUBSTANCES*

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More than 300 pure organic substances have been studied in detail by calorimetric methods. More than one-third of these compounds exhibit some type of thermal anomaly in the condensed phase. In 1940 Deffet[1] listed nearly 1,200 organic sustances in which polymorphism had been detected by either thermal or non-thermal methods, or both. Obviously, phase transformations other than melting are among the more common phenomena encountered in physical and thermodynamic studies of organic substances. Despite an abundance of experimental facts accumulated in the last 50 years, and despite the efforts of many able scientists to interpret these facts, satisfactory theoretical explanations of phase transformations in organic solids are rare.

Several recent reviews illustrate clearly the difficulties met in attempts to understand phase transformations either in terms of classical thermodynamic phase relations or of molecular and structural phenomena[2–4]. Theoretical treatments involving the use of statistical mechanics have yielded results in qualitative or, occasionally, quantitative agreement with experimental data for a few simple systems, most of which are composed of inorganic substances. So far these treatments are limited to two-dimensional cases, and even so, are quite complex. Partial interpretations of transitions of some molecular crystals have been made in terms of the order–disorder and structural transformations pre umed to occur, but the common lack of adequate structural information usually makes such interpretations only tentative.

One of the reasons for the seemingly slow progress in developing theoretical interpretations of phase transformations may be that the theorist cannot be sure as to the nature of the phenomena that he must explain. The experimental data on phase transformations are scattered in the literature and often are reported in a confusing way. Different authors use the same terminology for what appear to be different phenomena, or different terminology for what appear to be similar phenomena. The purpose of this paper is to present in brief outline a systematic classification of the types of transitions that occur in hydrocarbons and related substances as an aid in eliminating some of the present confusion.

CLASSIFICATION OF TRANSITION TYPES

Jaffray[2], among others, discussed the difficulty of classifying phase transformations by relating them to either the macroscopic (thermodynamic) or microscopic theories of such phenomena. He presented a classificaton based on the geometrical form of the free energy and entropy curves below, at, and above a transition point. The classification given here is essentially

* Contribution No. 82 from the Thermodynamics Laboratory.

that of Jaffray, but it is strictly phenomenological and includes some types not recognized as distinct by Jaffray. Because the classification is based entirely on observed heat capacity and enthalpy curves, only substances studied by calorimetric methods were considered.

From examination of results reported for the 95 compounds listed in *Table 1*, it was concluded that *seven* types of transformations in solid phases could be distinguished phenomenologically. Some of these types have been named in the literature, but the meanings attached to such terms as " first order ", " isothermal ", " second order ", " second kind ", " lambda ", and " higher order " are not uniform. For this reason, the types described in the following paragraphs are designated by numbers and/or letters so chosen as to have some mnemonic value.

Table 1. Solid–solid transitions in organic substances

Compound	*Transition type**	*Ref.*†
Saturated hydrocarbons		
Methane	3N	5
Monodeuteromethane	3N(2)	6
Deuteromethane	3N(2)	7
n-Butane	1	8
2,2-Dimethylpropane	2I	9
2,2-Dimethylbutane	1(2)	10
2,3-Dimethylbutane	3I	10
2,2-Dimethylpentane	3N	11
2,2,3-Trimethylbutane	3N(2), 1	11
2,2,3,3,-Tetramethylbutane	2I	12
n-Nonane	2I	13
2,2-Diethylpentane	H,1(2)	11
n-Undecane	2I	13
n-Tridecane	2I	13
n-Pentadecane	2I	13
Unsaturated hydrocarbons		
2-Butyne	2N	14
Polyisobutene	G	15
3,3-Dimethyl-1-butene	2I	16
2,3-Dimethyl-2-butene	1	17
1-Decene	1	18
1-Undecene	1	18
1-Dodecene	3I	18
1-Hexadecene	3N	18
Cyclic hydrocarbons		
Cyclobutane	2N	19
Cyclopentene	G, 3I	20
Cyclopentane	1, 3I	21
Cyclohexene	1	20
Cyclohexane	3I	22
1,3,5-Cycloheptatriene	G, 2I	23
Cycloheptane	1(3)	23
1,1-Dimethylcyclopentane	3I	24
1,*cis*-2-Dimethylcyclopentane	1	24
Cyclo-octane	1(2)	23
1,1-Dimethylcyclohexane	1	25
1,*cis*-2-Dimethylcyclohexane	G, 1	25
cis-Hexahydroindan	1(2)	11
cis-Decahydronaphthalene	G, 1	26
n-Decylcyclohexane	H	11

* The number of transitions of each type is shown in parentheses if more than one occur.
† Only the most recent reference is listed.

VOL. 2 1961

Table I—continued

Compound	*Transition type**	*Ref.*†
Aromatic hydrocarbons		
1,3-Dimethylbenzene	H	27
1,4-Dimethylbenzene	H	27
1,3,5-Trimethylbenzene	H	28
1-Methylnaphthalene	I	26
2-Methylnaphthalene	2I	26
Pentamethylbenzene	I	29
Hexamethylbenzene	3N, H	30
Oxygen compounds		
Methanol	3I	31
Acetone	H	32
Furan	2I	33
n-Butanoic acid	2N	34
1,4-Dioxane	I	35
Cyclopentanol	I, H	36
n-Pentanol	H	37
2-Methyl-2-butanol	I	37
l-Sorbose	2N	38
Benzyl alcohol	H	39
Sulphur compounds		
Methanethiol	I	40
Thiacyclobutane	3I	41
1-Propanethiol	I	42
2-Propanethiol	2I	43
Thiophene	H(2), 3I	44
2-Methyl-2-propanethiol	3I,I(2)	45
2-Methylthiophene	G	46
3-Methylthiophene	G	47
Thiacyclohexane	2I, 3N, I	48
2-Methyl-2-butanethiol	3N,2I	11
3,3-Bisthiaethyl-2,4-dithiapentane	I(2)	49
Benzenethiol	H	11
Cyclopentyl-1-thiaethane	3N, I	11
Benzo(b)thiophene	G, 2I	50
Miscellaneous compounds		
Carbon tetrabromide	2N	51
Carbon tetrachloride	2I	52
Carbon tetrafluoride	2I	53
Chlorodifluoromethane	H	54
Sodium methoxide	H	55
Methylamine	H	56
Methylammonium chloride	I(2)	57
Chloropentafluoroethane	I	58
Polytetrafluoroethylene	3N,H	59
1,1,1-Trichloroethane	2I	60
1,1,1-Trifluoroethane	2I	61
Sodium acetate	H	62
1,2-Dibromoethane	2I	63
1,2-Dichloroethane	H	63
Dimethylcadmium	I	64
sym-Dimethylhydrazine	G	65
Dimethylaminediborane	2I	66
Propenenitrile	I	11
Octafluorocyclobutane	G,3N,2N(3)	67
Pyrrole	H	11
Pyrrolidine	2I	11
Undecafluoropiperidine	2I,I	11
n-Pentylammonium chloride	3N(2)	68
n-Hexadecafluoroheptane	I	69
Copper(II) acetonylacetone	H	70

* The number of transitions of each type is shown in parentheses if more than one occur.
† Only the most recent reference is listed.

Type 1—The Type 1 transition illustrated in *Figure 1* is familiar as the so-called "isothermal" or "first order" transition, which is believed to occur entirely isothermally in the manner of melting for most pure substances.

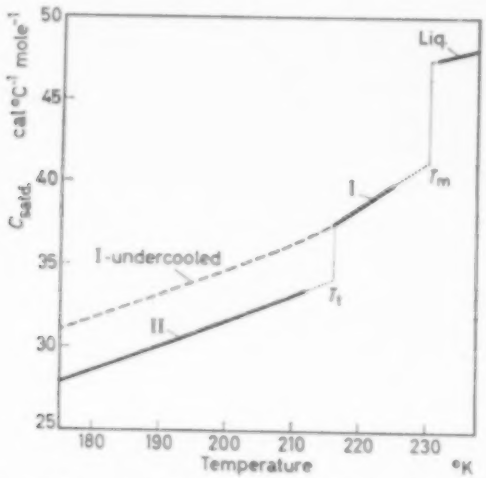

Figure 1. Type 1 transition in *cis*-decahydronaphthalene[26]: $T_m = 230{\cdot}18$°K, $\Delta H_m = 2268$ cal/mole; $T_t = 216{\cdot}1$°K, $\Delta H_t = 510{\cdot}6$ cal/mole

Thus, the heat capacity is "normal" immediately above and below the transition point, and the two crystalline phases involved are thermodynamically distinct. In fact, as the illustration shows, the high-temperature phase (crystals I) often may be undercooled, and occasionally the low-temperature phase (crystals II) may be superheated.

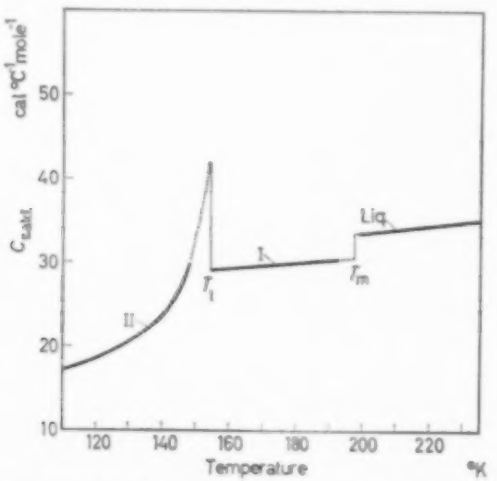

Figure 2. Type 2I transition in cycloheptatriene[25]: $T_m = 197{\cdot}92$°K, $\Delta H_m = 277{\cdot}4$ cal/mole; $T_t = 153{\cdot}98$°K, $\Delta H_t = 560{\cdot}9$ cal/mole

VOL. 2 1961

Type 2I—The Type 2I (isothermal) transition is characterized by an upsweep in the heat capacity curve below the transition temperature, at which the remainder of the transformation proceeds isothermally. The heat capacity is " normal " above the transition temperature. An extreme example of this type is given in *Figure 2*. In other cases, the " pre-transition" effect shown by the heat capacity curve of crystals II is much less pronounced. Also, the heat capacity of crystals I at the transition point may be either greater or less than that of crystals II. As a Type 1 transition resembles the melting of a *pure* substance, so the Type 2I transition resembles the melting of an *impure* substance.

Type 3I—Transitions of Type 3I, illustrated in *Figure 3*, differ from those in Type 2I only in that the heat-capacity variation for crystals I shows that transformation continues *above* the point of isothermal transition in addition to beginning below that point. Comparison of *Figures 2* and *3* shows that this distinction is real from a phenomenological viewpoint.

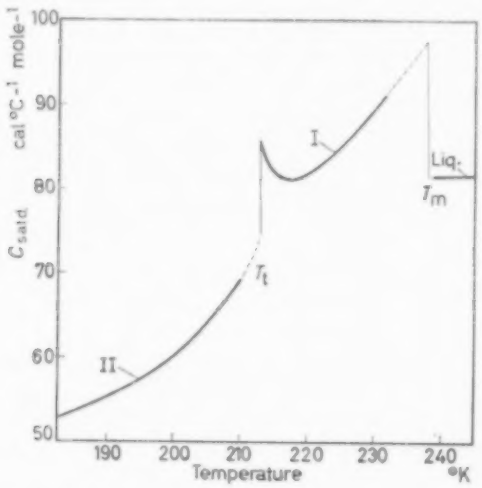

Figure 3. Type 3I transition in 1-dodecene[18]: T_m = 237·93°K, ΔH_m = 4758 cal/mole; T_t = 212·9°K, ΔH_t = 1088 cal/mole

Type 2N—Figure 4 is an example of a Type 2N (non-isothermal) transition, so designated because of its apparent resemblance to a Type 2I transition. However, although the heat capacity may reach very high values at the transition point, the Type 2N transition appears to be entirely *non-isothermal*.

Type 3N—The Type 3N and Type 3I transitions are related in the same manner as those of Type 2N and Type 2I. As illustrated in *Figure 5*, the Type 3N transition occurs over a range of temperature both above and below that at which most of the transformation occurs, but at no point does the process proceed isothermally.

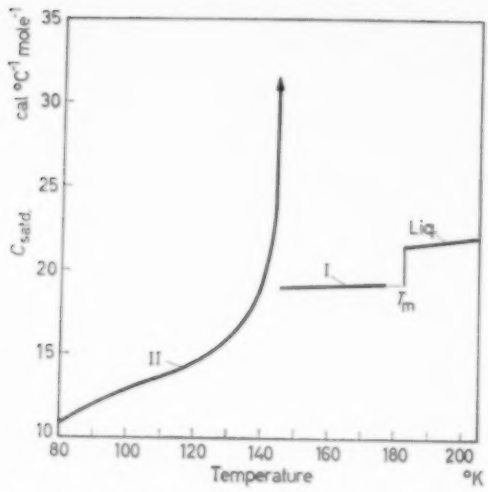

Figure 4. Type 2N transition in cyclobutane[19]: C_{max} = 876 cal °C^{-1}mole^{-1} at 145·54°K; T_m = 182·43°K, ΔH_m = 260·1 cal/mole

VOL. 2 1961

Type H—Transitions that are evidenced only by a maximum or " hump " in a continuous heat capacity curve are classed as Type H. The heat capacity curve shown in *Figure 6* is typical, but the hump often is much broader. The maximum heat capacity value usually is no more than twice the " normal " value.

Type G—Type G (glass-like) transitions, illustrated in *Figure 7*, are so designated because of their obvious resemblance to the glassy transitions

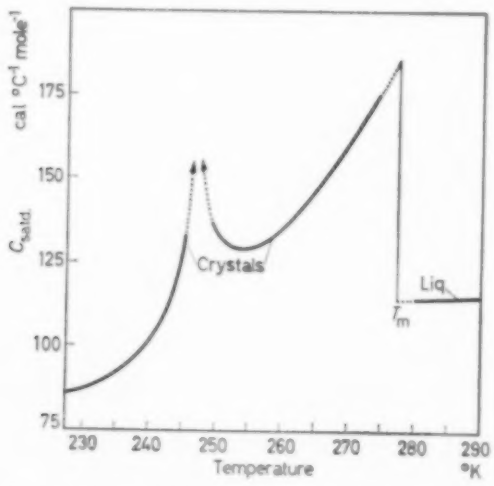

Figure 5. Type 3N transition in 1-hexadecene[18]: T_m = 277·51°K, ΔH_m = 7216 cal/mole

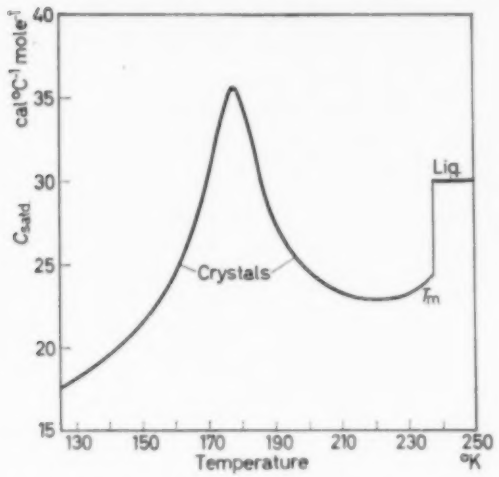

Figure 6. Type H transition in 1,2-dichloroethane[63]: $T_m = 237{\cdot}2°K$, $\Delta H_m = 2112$ cal/mole

that occur in some under-cooled organic liquids. Indeed, both the true glass transitions in liquids and the Type G transitions in solids probably involve the same kind of " freezing-in " of molecular degrees of freedom. In some solids, the Type G transition may be neither so sharp nor so large as that in *Figure 7*. Also, although the slight peak in *Figure 7* is similar to those observed in some studies of glasses, it may not be real.

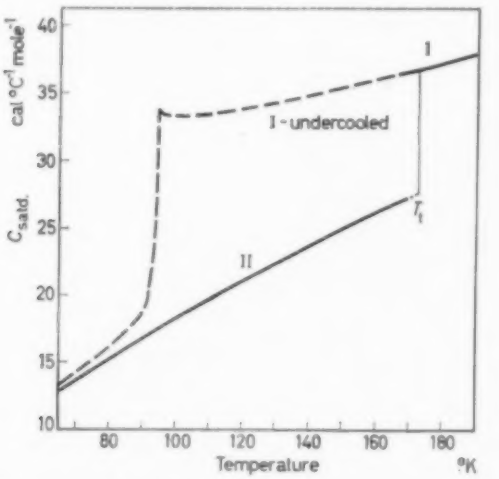

Figure 7. Type G transition in 1,*cis*-2-dimethylcyclohexane[25]: $T_t = 172{\cdot}50°K$, $\Delta H_t = 1973{\cdot}4$ cal/mole

DISCUSSION

The classification given here was made with only incidental attention to possible interrelationships among the several types or to theoretical explanations that have been advanced for some of the types. This approach provides a fresh point of departure for further study, but an evaluation of the distinctions that have been drawn is necessary. As knowledge of phase transformations increases, it is likely that the number of distinct transition types will be recognized as smaller than the number distinguished here. Such simplification most probably will be the result of theoretical developments, for experimental methods already have been pushed nearly to the limit of their power of discernment.

Two effects limit experimental elucidation of the nature of phase transformations. The first, which might be eliminated and which ought to be the subject of more study, is the effect of impurities. Solid-insoluble impurities may have little effect on solid–solid phase transformations, but solid-soluble impurities could have a pronounced effect. Scott *et al.*[12] showed that the transition temperature of 2,2,3,3,-tetramethylbutane varies in samples of different purity. The second effect, which may not be subject to elimination, is that of the slow thermal equilibration so common in organic crystals. Experience in this Laboratory and elsewhere has shown that thermal equilibration in the vicinity of transition points may require more than 72 hours. Thus, accurate heat capacity measurements in the region of a phase transformation may be impossible, and it may not be feasible even to determine whether or not a transition is isothermal. The dotted portions of the curves in *Figures 1–7* indicate regions in which reliable heat capacity measurements could not be made.

The limitations of experimental investigations are responsible for some arbitrariness in this classification. There may be no real difference between transitions of Types 2I and 2N, Types 3I and 3N, or even Types 3N and H. On the other hand, *phenomenologically* similar types may be quite different in terms of detailed transformation processes. Thus, any theory or theories of phase transformations must account for both the *apparent* differences and the *apparent* similarities among the transition types that have been observed in hydrocarbons and related substances.

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VOL
2
1961

MOLECULAR FREEDOM IN SOLID SOLUTIONS OF HYDROCARBONS: SOME OBSERVATIONS ON POSSIBLE CAUSES OF SELF-DIFFUSION

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INTRODUCTION

Crystals of complex molecules which are highly spherical in shape have unusual properties for a considerable range of temperature below the melting point, as was first recognized by J. Timmermans who called such compounds " molecules globulaires ". While the melting point is sharp, the condensed phase below the melting point is not crystalline in the strict sense of the word.

The reflections of X-rays from the planes are much more diffuse than the reflections from the planes of the usual crystal[2, 3]. However, their reflections indicate a highly symmetrical arrangement of the centres of gravity of the molecules.

It has now been shown that in such crystals the molecules are more or less free to rotate and that there is also self-diffusion as in liquids. For this reason this writer prefers to call them plastic crystals (not to be confused with *liquid* crystals).

Because of the mobility in plastic crystals, " molecules globulaires ", when in such a state, are mutually soluble. The present paper compares the properties of the solid solutions formed in the plastic crystal with the properties of the components in an attempt to throw further light on the origin of their peculiar properties.

PROPERTIES OF PURE PLASTIC CRYSTALS (ONE COMPONENT)

Phase changes

On cooling plastic crystals to low temperatures they undergo one or more transitions in which rotation and migration stop. Examples of such transitions are given in *Table 1*, where the corresponding latent heat is given below the temperature. It should be noted that the plastic crystals in all cases have sharp, well defined, melting points with considerable heat of fusion. However, sometimes they pass into a phase which is quite analogous to a glass. Such a condition will be discussed later.

The transitions may be of the first order or of the second (or higher order). It is an almost universal rule that if the molecule approximates spherical symmetry (*e.g.* methane, carbon tetrachloride, *etc.*) sufficiently closely, the transition in which most of the rotation is lost will be second order. The corresponding transition will be first order if the molecule approximates an

Table 1. Data on solid and liquid phases of " molecules globulaires "

Compound	*Measured line widths**			*Calculated line widths* (G)		*Transition temperatures* (°K)		*Melting temp.* (°K)	*ΔS of fusion* (cal °C^{-1} mole^{-1})
	I	II	III†	*Rigid*	*Rotating*	*Lower*	*Upper*		
Methane[6]	~ 7(a)	~ 7 → 0(a)	—	16(a)	14(a)	20(S) 157‡	—	90·0	2·47
Carbon tetrafluoride[7]	~ 13(b)	~ 0·5 → 0(b)	—	12(b)	< 1·50(b)	76(S) 354‡	—	89·5	1·84
Perfluoroethane[8]	~ 15(b)	~ 1·2 → 0(a)	—	> 7·5(b)	—	104(S) 893‡	—	173·0	3·70
Carbon tetrachloride[9]	—	—	—	—	—	225(S) 1095‡	—	250·3	2·40
Tetramethylmethane[9, 10]	2·5(a)	2·5(a)	—	—	—	140(S) 616‡	—	256·0	3·03
Cyclohexane[11, 12]	26 → 6·4(b)	1·4(b)	—	—	—	186(S) 1598‡	—	279·8	2·24
2,2-Dimethylbutane[13]	9(a)	2·3 → 0·4(a)	0·4(a)	—	—	127(F) 1289‡	141(F) 68‡	174·2	0·79
Cyclopentane[14]	26(b)	0·8 → 0·2(b)	0·3 → 0(b)	28·0(b)	1·7(b)	122(F) 1165‡	138(F) 83‡	179·7	0·80
2,3-Dimethylbutane[13a]	~ 9(a)	—	—	—	—	136(F) 1552‡	—	145·2	1·32
tert-Butyl chloride[15]	4·0(a)	4·0(a)	0·5(a)	16(a)	—	183(S) 410‡	220(S) 1390‡	248·2	1·90

* Width at half the (a) peak height (G), or (b) second moment (G^2).
† I denotes solid phase stable at low temperature. II and III denote solid phases respectively stable at increasingly higher temperatures.
‡ Heat of transition in cal/mole.

VOL
2
196

oblate spheroid (*e.g.* cyclopentane) or is pear-shaped (*e.g.* 2,2-dimethylbutane). In *Table 1* the transition temperature is marked (F) if the transition is first order and (S) if the transition is second order.

Dielectric constants of the phases

It was early recognized by Smythe and co-workers[4] that when a liquid composed of polar molecules froze to yield a plastic crystal, the dielectric constant suffered no sharp fall analogous to that which occurs when rotation is not possible. Indeed, later they devised an apparatus for measuring dielectric constants and heat capacities simultaneously[5]. With this, they showed, for example, that *tert*-butyl chloride had two transitions, the upper being second order and with the higher heat. On cooling it was at the upper transition that the sharp fall in dielectric constant occurred.

Nuclear magnetic resonance line broadening

Gutowsky and Andrew together with their co-workers have studied the effect of rotation in the solid state on the shape of the nuclear magnetic resonance absorption line. The observed shapes may be compared with values calculated from theory. A line which is broad below a rotational transition will become narrow above the transition. However, a line may become narrow owing to flipping of methyl groups over the barrier hindering rotation. Also, as in the case of methane, the arrangement of the proton spins in the non-rotating form may be such as to produce a line so narrow that the rotation of the molecule above cannot produce significant narrowing. Thus, the shape of the nuclear magnetic resonance line is not always as obvious a criterion of rotation as the dielectric constant. The method of nuclear magnetic resonance has the advantage that it can be used with non-polar molecules and that the measured line shape can be compared with one calculated theoretically on the basis of postulated models. *Table 1* summarizes the transition temperatures and the nuclear magnetic resonance line width for a number of solids.

Self-diffusion in plastic crystals and its origin

Comparison of measured line shapes with those calculated from theory has shown that cyclopentane after passing through the lower transition undergoes self-diffusion in the crystal, as well as rotation, whereas carbon tetrafluoride shows no evidence of self-diffusion till the melting point is reached, while methane only shows evidence of self-diffusion when the rotating crystal is close to the melting point. In the case of cyclohexane the nuclear magnetic resonance shows rotation but no self-diffusion immediately above the rotational transition. Half-way towards the melting point only does the line narrow to values which indicate self-diffusion. Inspection of models makes it evident that the envelope over the general shape of cyclopentane is roughly an oblate spheroid, whereas for cyclohexane a similar envelope is almost spherical. The nuclear magnetic resonance measurements[15] on *tert*-butyl chloride confirm the conclusions from the dielectric constant measurements, namely that it is at the upper second order transition that most of the rotation begins.

The graph of heat capacity as a function of temperature for cyclopentane which is given in *Figure 3* shows that the first transition, where most of the rotation sets in, is first order, as also is the second.

It should be noted that in the usual case the heat capacity curve for a liquid at the melting point is considerably above that of the crystal immediately below the melting point when the crystal is a true crystal. Thus, in the case of a first order rotational transition the heat capacity of the rotating phase immediately above the rotational transition should be considerably higher than that of the non-rotating phase.

The argument for this is that apparently where the transition is first order (oblate spheroidal or pear-shaped molecules) rotation and migration set in simultaneously producing a sufficiently high degree of co-operation to make the transition first order. Thus, the situation is similar to that at the melting point of an ordinary crystal. The heat capacity curve of cyclopentane shown in *Figure 3* is in agreement with this prediction.

When the transition is second order (almost spherical molecules) except for the immediate neighbourhood of the transition, the curve for the rotating solid is almost a continuation of that of the non-rotating solid. In the case of almost spherical molecules it is only rotation that sets in at the rotational transition. There is no translation; thus, the transition is not as sharp as when self-diffusion sets in simultaneously.

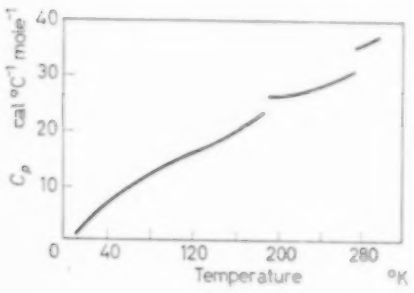

Figure 1. The heat capacity of cyclohexane

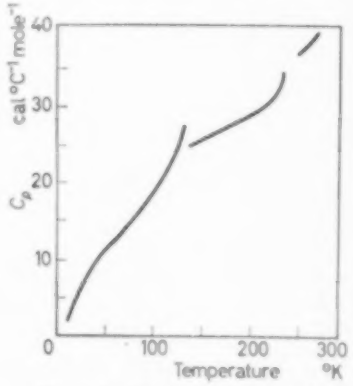

Figure 2. The heat capacity of tetramethylmethane

Cyclohexane is a good example. The curve of heat capacity against temperature shown in *Figure 1* has a transition. On the low temperature side of the transition the abnormal rise in the heat capacity is evident, although not very pronounced. The striking thing is that the heat capacity for the solid above the transition is almost a continuation of that below. This is in accord with the nuclear magnetic resonance data. Comparison with the corresponding heat capacity curve of tetramethylmethane given in *Figure 2* indicates that cyclohexane is similar to tetramethylmethane, whose molecules have a spherical envelope, and cyclopentane is not similar (see *Figure 3*).

The entropies of fusion given in the last column in *Table 1* are a striking confirmation of these conclusions. Monoatomic crystalline solids, on fusion,

gain the communal entropy of R. Compounds with no rotational transitions (where rotation sets in on melting) have an entropy increase several times R, because they gain rotational as well as translational entropy on fusion. Examples are n-butane and n-pentane whose entropies of fusion are 8·3 and 14·0 cal $°K^{-1}$ $mole^{-1}$. Compounds with second order rotational transitions have an entropy of fusion of about R, which is the increase in communal entropy, whereas those showing first order transitions have considerably lower entropy of fusion. When a solid is rotating, it only has to gain its communal entropy of fusion. If, on the other hand, the solid has some translational freedom as well as fully excited rotation, some of the communal entropy has already been gained before melting. Thus the entropy change is smaller than R.

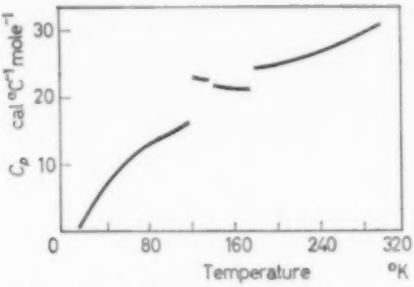

Figure 3. The heat capacity of cyclopentane

SOLID SOLUTIONS AND MIXTURES

Systems with spherical molecules

It is natural to expect from what has just been said about spherical molecules, that krypton, whose atoms have about the same atomic diameter as the molecules of methane, would form solid solutions with it. This is indeed the case. It would also be expected that the truly spherical nature of the krypton diluting atoms would make it easier for methane molecules to rotate. For pure methane, when one molecule starts to rotate it is easier for another molecule to do so. If krypton is present there is no similar rotation of krypton atoms to assist. Thus, the effect of krypton should be

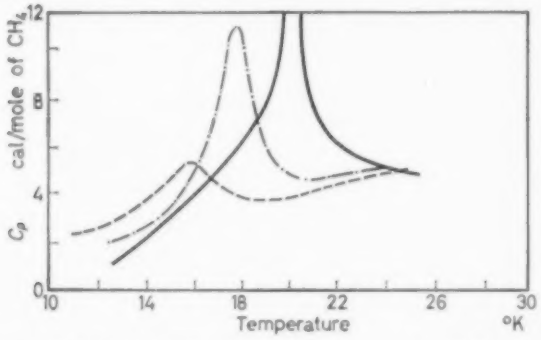

Figure 4. Methane diluted with krypton: — 0%Kr; — · — 7·45%Kr; – – – 15·60%Kr

to decrease the degree of co-operation and to make the transition of higher order than second. Eucken and Vieth[16] have studied the heat capacities of solutions of krypton in methane. Their results, which are shown in *Figure 4*, constitute a striking verification of the predictions.

A further verification of the factors causing rotation in the solid state is obtained by examining the heat capacities of methane adsorbed on a surface. Steele[17] has found that the transition is present in methane down to a coverage of two layers. At this coverage the λ transition has only been lowered by 0·3°. This effect is understandable when one notes that below 17°K the heat capacities for less than two layers are considerably smaller than those of the systems showing lambda transitions. This means that the molecules are rotating more or less freely in the monolayer (classical heat capacity $R/2$, as compared with R for vibration). For two layers this is presumably true for the outer one. The lambda point above two layers involves only rotation in the inner layers, which should not differ much from that in the bulk.

Incomplete nuclear magnetic resonance measurements on methane[18] have been carried out in the writer's laboratory for the purpose of supplementing the heat capacity data. While the accuracy of the data at the low coverages is questionable, the data at four monolayers seem to verify the conclusions from the heat capacities. These measurements are, of course, being repeated.

VOL. 2 1961

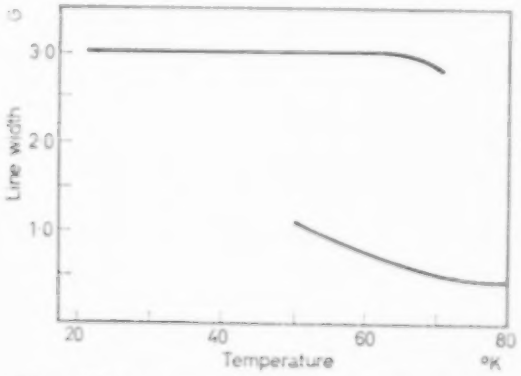

Figure 5. Line width *versus* temperature for one monolayer of CF_4 on TiO_2

Nuclear magnetic resonance studies have been made on carbon tetrafluoride adsorbed on high-area titanium dioxide[7].

In *Figure 5* are shown graphs of the line width (at half the peak height) *versus* temperature of the narrow and broad components of the line for one molecular layer on the surface. The narrow component is due to rotation which does not cease above 20°K. This confirms the fact that in order to prevent rotation at any temperature a full complement of nearest neighbours in all three dimensions as in a crystal is necessary. A full complement of neighbours in a plane will not do. This confirms results obtained for diatomic gases at Oxford[19, 20].

Carbon tetrachloride and *tert*-butyl chloride form a continuous series of solid solutions[4] with a minimum in the melting point diagram at 50 mole-

per cent. The rotational transition for the 50 mole-per cent solid solution is at 231°K which is above the upper rotational transition of *tert*-butyl chloride, as well as above the rotational transition of the carbon tetrachloride. In this case there is no reason to expect that rotation of either component would be easier in the mixture. The fact that there is a minimum in the melting point diagram at 50 mole-per cent would lead one to expect a somewhat closer packing in the rotating solid solution than in the rotating crystal of either component and hence a somewhat higher temperature for the rotational transition.

Systems with non-spherical molecules

Two binary systems involving non-spherical molecules have been investigated, namely: (A) 2,2- with 2,3-dimethylbutane[22] and (B) 2,2-dimethylbutane–cyclohexane[23, 21].

In the case of the first of these systems there is a maximum in the melting point diagram at 0·40 mole 2,3-dimethylbutane and 0·60 mole 2,2-dimethylbutane. This mixture has a sharp melting point and presumably indicates some preferred crystal arrangement (complex).

The heat capacity[22] is shown in *Figure 6* along with the N.M.R. line width. The melting point is sharp. Below the melting point the heat capacity curve resembles that of a glass, there being a slight peak after the rapid rise in heat capacity characteristic of the softening of a glass. This peak is accompanied by a decrease in N.M.R. line width from 8 to 2 gauss. The entropy change on melting is[22] 1·61 cal/°K per mole of mixture (*i.e.* 0·40 mole 2,3-dimethylbutane and 0·60 mole 2,2-dimethylbutane). This is considerably higher than the normal entropy of fusion of either component. On the basis of the qualitative correlation of the pure components one would suspect that the rotational transition would be second order. Unfortunately no rotational transition is observed owing to the supercooling to a glass.

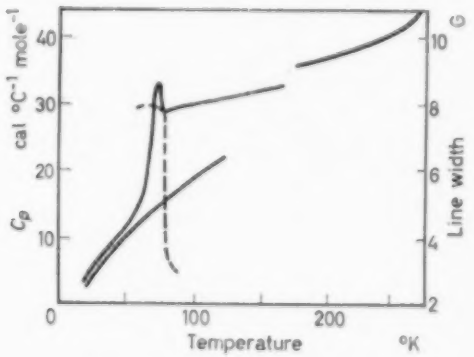

Figure 6. Heat capacity and N.M.R. line width of 0·4 mole 2,3-dimethylbutane and 0·6 mole 2,2-dimethylbutane: — heat capacity; – – line width

The data on the 2,2-dimethylbutane–cyclopentane system definitely confirm this conclusion. In this system there is a maximum in the melting point curve at 0·33 mole 2,2-dimethylbutane and 0·67 mole cyclopentane.

The heat capacity[23] curve for this mixture is shown in *Figure 7*. Here again the melting point is sharp. There is no tendency to supercool, and the rotational transition can be observed. In place of the two transitions for each component there is a single transition at 83°K. This transition is second order. The entropy of fusion is 1·45 cal/°K per mole of mixture (0·333 mole 2,2-dimethylbutane and 0·667 mole cyclopentane). This is considerably higher than the molal entropy of fusion for either of the components.

The width of the N.M.R. line as a function of temperature is also shown in *Figure 7*. There is a narrowing from 12 G to 3 G at about 65°K, where the abnormal rise in heat capacity preceeding the transition starts. This value of 3 G is of the order of that expected for rotating molecules with fixed centres. It is only near the melting point that the line narrows to 1 G, indicating self-diffusion.

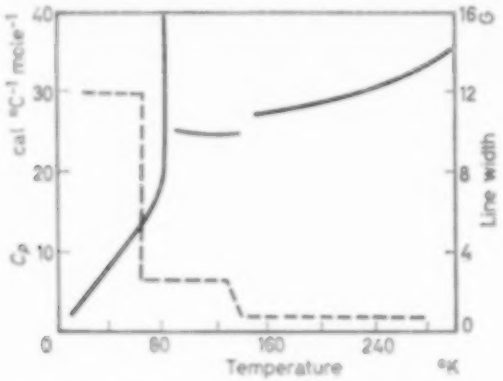

Figure 7. Heat capacity and N.M.R. line width of 0·333 mole 2,2-dimethylbutane and 0·667 mole cyclopentane

The fact that the transition occurs at a temperature forty degrees below the lowest transition of either component indicates that there is some sort of favoured unit (complex) of 1 mole of 2,2-dimethylbutane to 2 moles of cyclopentane which rotates in the crystal more easily than does either component. This unit would be expected to have high symmetry, to rotate with such ease. This is in keeping with the fact that the transition is second order. The fact that the average entropy of fusion is nearer R per component molecule than that for either component means that the 2,2-dimethylbutane and cyclopentane molecules gain almost their full communal entropy on melting. This indicates little self-diffusion in the rotating crystal, in keeping with the N.M.R. data. In molecules with almost spherical envelopes there is little self-diffusion.

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VOL. 2 1961

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VOL.
2
1961

ORDERING TRANSITIONS IN SYMMETRICAL MOLECULES

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INTRODUCTION

Since Pauling's[1] original suggestion that certain types of solid–solid transitions might be explained by the onset of rotation in the crystalline state, many investigations have been carried out in an attempt to determine the nature of the mechanism of such transitions. Although originally the rotational freedom was attributed only to relatively simple molecules, Smyth[2, 3], through extensive investigations of the dielectric constants of compounds showing transitions, extended Pauling's view to include many larger and more complex molecules.

Perhaps the most extensive investigations have concerned the transitions in the ammonium halides. Apart from methane and some diatomic molecules, which are extremely difficult to study experimentally because of the low temperatures necessary for investigations, these compounds were considered to have the greatest probability of rotation in the solid state[1, 3]. Recent neutron diffraction investigations on the deuterated ammonium halides[4, 5], however, indicate that these transitions are explained as well by an order–disorder type of mechanism as by a rotational one[6]. Examination of the data for other compounds having solid–solid transitions shows that the results of experimental work in general neither prove nor disprove the existence of rotation in the solid state, but are equally consistent with the order–disorder mechanism for the transitions. Precise treatment of specific solid–solid transitions is greatly hindered by lack of accurate structural data, especially in the low-temperature region. These compounds are examples of relatively simple transitions because of the symmetry features of the ammonium ion.

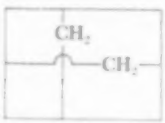
In solid–solid " pseudo-rotational " transitions in general, however, the structures, both molecular and crystallographic, are so complicated that no adequate correlation has been demonstrated between the isothermal entropy increments and structure changes at the transition temperatures. In transitions involving more complex molecules, the factors to be considered are apparently more convenient to study because of the larger number of possible comparison compounds which may be synthesized.

Two types of symmetrical molecules were considered to be of special interest at the outset of our researches on this interesting problem. Professor Isamu Nitta directed our attention to his extensive studies on pentaerythritol and to the pseudo-rotational problem in general. Dr Donald H. Payne (now of E. I. du Pont de Nemours) collaborated in this work and completed his doctoral thesis on compounds of the general type $C(CH_2X)_4$ (where X may represent halogen or hydrogen atoms, or hydroxyl groups).

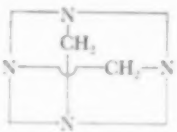
Solid–solid transitions have been studied in neopentane, $C(CH_3)_4$, by Aston[7] and in pentaerythritol, $C(CH_2OH)_4$, by Nitta[8–11]; the latter compound has a remarkably high entropy of transition. Comparison of the symmetry features of the high-temperature cubic modification of pentaerythritol with the symmetry features of neopentane, $C(CH_3)_4$, suggested that the symmetrical tetrahalide homologues of pentaerythritol would be interesting compounds for investigation. Although no transitions were reported in the literature for pentaerythrityl chloride, bromide, or iodide, synthesis of the pentaerythrityl fluoride, $C(CH_2F)_4$, was expected to produce a compound showing a low-temperature transition with a transition entropy increment intermediate between that of pentaerythritol and that of neopentane. Although the transition in pentaerythritol occurs at 180°C, the fluorine analogue should have a transition in the relatively low temperature region (below room temperature) because of the absence of the strong hydrogen bonds present in pentaerythritol.

The primary purpose of the problem investigated by Dr Payne, therefore, was the study of the low-temperature thermodynamic properties of the pentaerythrityl fluoride relative to the nature of the transitions occurring in the general compounds $C(CH_2X)_4$. By measuring the entropy for the predicted transition in this compound it was hoped to provide data for comparison with pentaerythritol and neopentane relative to the mechanism of the transitions in these compounds, in addition to the possible indication of a more general correlation applicable to this type of solid–solid transition.

Compounds of a second type are being studied by Mr Shu-Sing Chang. These are the unusual globular molecules such as the hydrocarbon adamantane (A), hexamethylenetetramine (B), and related organic molecules with nitrogen, sulphur, oxygen, and phosphorus substituted into the cage structure.



(A)



(B)

These compounds are characterized by extremely high melting points for organic solids (e.g., 270°C for adamantane) and probably by low entropy increments on fusion. Moreover, from the point of view of the chemist, the loss of the high symmetry factor in compound or complex formation provides an additional driving force in chemical reactions. An energetic transition was discovered at 208·6°K in adamantane soon after a synthetic method for the preparation of this substance became known to us.

THE CALORIMETRIC APPARATUS

The Mark I cryostat for use over the range 4°–350°K was an improved version of one constructed by Westrum, Hatcher, and Osborne[12]. Liquid helium was used as the lowest temperature refrigerant, and a thermal conduction resistance (called the " economizer ") was provided to take advantage of the relatively large cooling potential of the enthalpy of gaseous helium

VOL. 2 1961

(compared with the heat of vaporization). The adiabatic method of operation was employed.

The gold-plated copper calorimeter (Laboratory Designation W–6) used for the pentaerythritol derivatives was 3·8 cm in diameter and 7·7 cm long with a shell thickness of 0·4 mm. Eight radial vanes of 0·1 mm copper foil aided in establishing thermal equilibrium. A re-entrant gold-plated copper heater well contained a platinum capsule-type resistance thermometer, calibrated by the National Bureau of Standards, within a cylindrical copper heater sleeve carrying 160 ohms of B. and S. No. 40-gauge Advance (constantan) double-fibreglass insulated wire, which was wound bifilarly in double-threaded grooves and cemented in place with " Formvar ". Calorimeter W–6 differs from the usual calorimeter in that a special Monel neck of 15 mm diameter partially isolates the actual lid from the copper calorimeter, and thus allows the lid to be soldered in place with "Cerroseal" solder without appreciably heating the calorimeter or the samples which are placed therein. Calorimeter W–9, used for the adamantane-like compounds, is essentially similar, except that only four vanes are employed. The calorimeter was also tested by measuring the heat capacity of a standard sample of benzoic acid.

RESULTS OF THE CALORIMETRIC INVESTIGATIONS

Table 1 provides a summary of the 298·15°K values of the molal heat capacities and thermodynamic functions of the five $C(CH_2X)_4$ compounds studied. Details of the preparation, purification, and characterization of the samples used in these investigations will be reported in a subsequent publication.

Although little of unusual nature was manifest in the other four compounds, a sharp lambda transition of considerable magnitude was found at 249·40°K in $C(CH_2F)_4$, with a heat of transition of 3157·5 ± 2·3 cal/mole and a molal entropy of transition of 12·7 cal $°K^{-1}$ $mole^{-1}$. The data are also presented graphically in *Figure 1*.

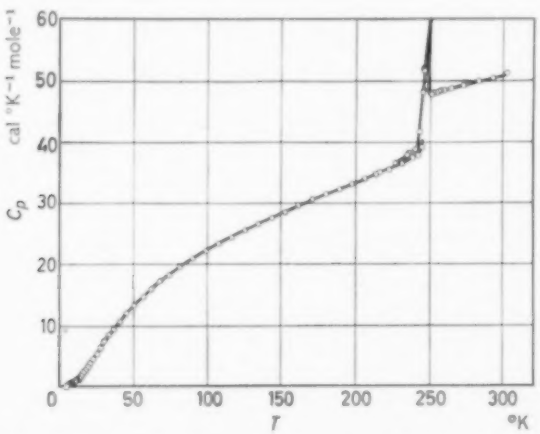


Figure 1. The heat capacity of pentaerythrityl fluoride

Table 1. Thermodynamic functions at 298·15°K for the crystalline solids (in cal °K^{-1} mole^{-1})

	C_p	S°	$-\frac{F^\circ - H_0^\circ}{T}$
$C(CH_2OH)_4$	45·51	47·34	23·16
$C(CH_2F)_4$	50·80	69·35	31·33
$C(CH_2Cl)_4$	47·44	61·54	32·22
$C(CH_2Br)_4$	51·10	69·58	39·45
$C(CH_2I)_4$	49·64	75·70	43·97

For adamantane, a sharp lambda-type transition involving 3·9 e.u. was found at 208·6°K. At 298·15°K the heat capacity, entropy, enthalpy increment, and free energy function are 45·46 cal °K^{-1} mole^{-1}, 46·80 cal °C^{-1} mole^{-1}, 7270 cal/mole, and − 22·42 cal °K^{-1} mole^{-1}, respectively.

DISCUSSION

Perhaps the important group of transitions which result primarily from an orientation of the molecule itself within the crystal structure may loosely be described as " pseudo-rotational " in nature. Only such transitions are presently under consideration. That volume increments, *etc.*, may also result from such transitions is, of course, evident. Before attempting to interpret the data concerning the compounds investigated in this research, and the data available from other sources, it is desirable to consider first what type of relationships should be expected from " pseudo-rotational " transitions in general.

The fusion phenomenon has been discussed by several authors[13, 14] who have shown that the correlations existing between fusion entropy increments are not as clear as would be desired. For elements or simple molecular-type compounds, the entropies of fusion generally lie between 1 to 3 e.u. The entropies of fusion for specific families of elements or classes of compounds existing in the same lattice classification can generally be compared favourably within 0·3 to 0·4 e.u., while the comparisons differ more significantly for such elements or compounds in different lattices.

The disagreement observed in the fusion entropies of similar elements or analogous compounds has generally been attributed to one factor[15]. The lattice structure of any crystal system is dominated by a high degree of long-range order, if the crystal imperfections are not serious. In the process of fusion, the long-range order disappears in favour of a so-called short-range order, which is characteristic of liquids in general. Unfortunately, the short-range order attributed to liquids is apparently not uniform for all liquids, in contrast to the essentially identical degree of long-range order in the crystalline solids. The degree of short-range order is apparently dependent on the size and shape of the atoms or molecules in the liquid state, and on the forces arising from the nature of the element or compound in question. For a homologous series of compounds or a chemically similar series of elements, the discrepancies in the fusion entropies are usually not greater than 0·4 e.u.

VOL. 2 1961

Although solid–solid transitions, in contrast to solid–liquid transitions, may involve changes of lattice types, or orientational changes of particular molecular or ionic groups within the crystal, or both, the over-all degree of long-range order of the crystal structure, in general, persists both before and after the transition. Therefore, the type of entropy discrepancies attributed to differing degrees of order in the liquid state should not appear in the factors contributing to the entropy change found in low-temperature transitions. Consequently, in the "pseudo-rotational" transitions, the entropy associated with the change occurring in the symmetry features of the structure, both molecular and crystallographic, should be in agreement with the entropy calculated statistically from the change in the number of symmetry features involved in the transition. Support for this hypothesis is a goal of this research.

Nitta's interpretation of pentaerythritol

On the assumption of the above hypothesis, Nitta's treatment of the mechanism of the transition occurring in pentaerythritol[11] originally led to interest in the pentaerythritol transition. It is worthwhile to consider Nitta's approach to the problem before discussing the correlation with experimental results obtained in this laboratory.

First of all, the possibility of complicating positions of the hydroxyl hydrogen atoms in the hydrogen bonds due to a double minimum type of bond is neglected, and the configurational entropy of the low-temperature tetragonal phase of pentaerythritol is assigned the value zero. In the high-temperature cubic phase, however, the configurational entropy due to hydrogen and oxygen is of primary importance and must be taken into consideration. To estimate the entropy due to the hydrogen and oxygen, Nitta assumed, for convenience, a relatively simple model. Assuming three potential minima for a hydroxyl hydrogen atom rotating about a carbon–oxygen bond, as in the case of methanol, and also assuming that each such hydrogen atom is in motion independent of the motions of the rest of the molecule, the contribution due to the hydrogen atom positions is $4\,R\ln 3$. Each of the oxygen atoms is also assumed to have three potential minima about the carbon–carbon bond. However, the positions of the oxygen atoms in the molecule, where the oxygen atoms have very near approach to each other, are considered unlikely, and are omitted from calculation. Thus Nitta considers it possible that, in the cubic phase, there are three relatively stable configurations for the molecule as a unit. Each of these configurations has three orientational possibilities and a value of $R\ln 9$ is assigned for the configurational entropy due to the oxygen atoms in the molecule. Taking further into account that the crystallographic data indicate that the —CH_2O— tetrahedra have two configurations, Nitta assigns an additional factor of $R\ln 2$ for this effect. The total configurational entropy of the cubic phase due to hydrogen and oxygen is then, according to Nitta, $R\ln 9 + R\ln 2 + 4\,R\ln 3 = 14{\cdot}47$ e.u.

The entropies of transition and fusion of pentaerythritol are, respectively, 22·8 and 3·2 e.u. These were added and the entropy of fusion of pentaerythrityl bromide, 12·69 e.u., was subtracted, and the resulting value (13·3 e.u.) was compared with the configurational entropy of 14·47 e.u. calculated

above. Nitta states that " the agreement is rather unexpectedly close, for it is evident that the above estimation has been carried out in too simple a fashion . . . ". A disagreement of 1·1 e.u. is, however, greater than would be anticipated on the basis of the hypothesis discussed, if the proper mechanism had been employed.

Interpretation of pentaerythrityl fluoride

At the time this research work was initiated, only two symmetrically similar comparison substances, neopentane, $C(CH_3)_4$, and the tetramethyl ester of thiocarbonic acid, $C(SCH_3)_4$, had been investigated. Extensive studies carried out on these compounds showed a low-temperature transition in the neopentane, and two transitions below the melting point in the thiocarbonate. Although these two compounds are structurally similar to pentaerythritol, it was felt that a more ideal comparison substance would be found by synthesizing and investigating the properties of pentaerythrityl fluoride. Because of the proximity in size of oxygen and fluorine, it was anticipated that this compound would show a transitional behaviour similar to that of pentaerythritol except for the contributions of the hydroxyl hydrogen atoms. In fact, if the convenient assumptions:

(1) that both pentaerythritol and pentaerythrityl fluoride have the same degree of order in the low-temperature phase, and

(2) that by virtue of nearly equal size, oxygen and fluorine will occupy identical sets of positions in their respective molecules in the high-temperature phases,

are entertained, then the transitional entropy increments of pentaerythritol and of the fluoride would be expected to differ only by the hydroxyl hydrogen contribution. This contribution would be expected to give an increment of $4R \ln 3$ from the three positions of minimum energy for each of four hydroxyl hydrogen atoms. However, Nitta's Fourier analysis of the cubic phase of pentaerythritol indicates that the best agreement with the experimental data is obtained if the $-CH_2O-$ tetrahedra are allowed to have two sets of positions, one 180° out of phase with the other. For these two sets of positions for the $-CH_2O-$ tetrahedra there are two independent sets of 3^4 possible orientations for the hydroxyl hydrogen atoms in pentaerythritol and the entropy contribution should be $R \ln 2 + 4R \ln 3 = 10{\cdot}15$ e.u. If this value is subtracted from the measured transition entropy increment of pentaerythritol (22·8 e.u.), the difference is the calculated value for the transition entropy increment for pentaerythrityl fluoride (12·65 e.u.). The measured value for the pentaerythrityl fluoride transition is 12·66 e.u., in exact agreement with the calculated value.

Further interpretation of $C(CH_2X)_4$ molecules

This remarkable agreement suggested that it might be possible to account for the symmetry features involved in the entropy increment of 12·66 e.u. for the transition occurring in the fluoride. Since the contribution due to the hydroxyl hydrogen atoms in pentaerythritol has now been eliminated, a general model may be used for consideration of the fluoride, since it is fundamentally a pentaerythritol-like molecule without the hydroxyl hydrogen atoms.

VOL. 2 1961

Fischer–Hirschfelder models show that there are seven independent molecular structures for pentaerythritol resulting from all possible orientations of the oxygen atoms, but neglecting the positions of the hydroxyl hydrogen atoms. These seven molecular forms are shown in *Figure 2.* All of the molecular forms except I and II involve oxygen–oxygen approach, which is much too close to allow stability. I and II and the enantiomorph of II, however, are models where all oxygen–oxygen distances are large. Therefore, these are considered to be the only three stable molecular forms.

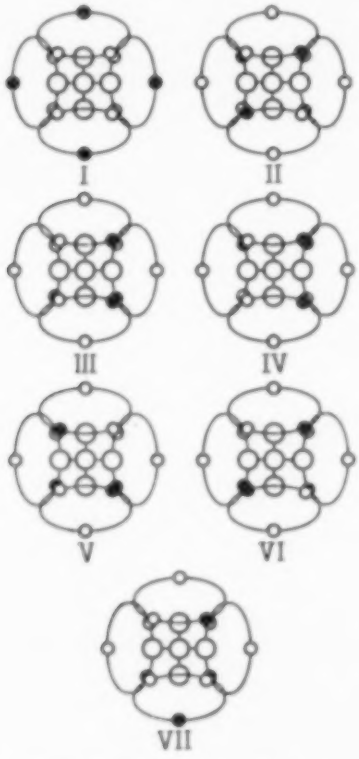


Figure 2. Seven molecular structures of pentaerythritol

The indication that two sets of positions are possible for the —CH_2O— tetrahedra in pentaerythritol may logically be extended to the —CH_2F tetrahedra in the fluoride. These two sets of positions can be conveniently described as " staggered " or " eclipsed " relative to the skeletal carbon–carbon bonds. No proof can be offered, of course, at the present time that the equilibrium positions do not deviate from these arbitrary choices.

Consider that all the tetrahedra occupy the same set of positions. By reasoning analogous to that employed on pentaerythritol, it is concluded that only three distinct, stable molecular forms exist wherein close approach

of the fluorine atoms to each other is not involved. It is assumed, but not demonstrated, that in single molecules in which some of the $—CH_2F$ tetrahedra occupy different sets of positions, two stable molecular forms will also exist. If each $—CH_2F$ tetrahedron can occupy two sets of positions, then, for four such tetrahedra, the number of configurations of the molecule in the crystal due to these orientations will be 2^4. For each one of these 2^4 molecular configurations, there will be, upon neglecting the positions of closest approach for the fluorine atoms, three distinct stable molecular forms, as assumed above, due to the presence of the fluorine atoms in the molecule. Therefore, there are 3×2^4 stable oriented molecular structures possible in the high-temperature phase. The entropy contributions due to these factors are, therefore, $R \ln 3$ for the presence of fluorine in the molecule and $4\ R \ln 2$ for the orientational possibilities of the $—CH_2F$ tetrahedra.

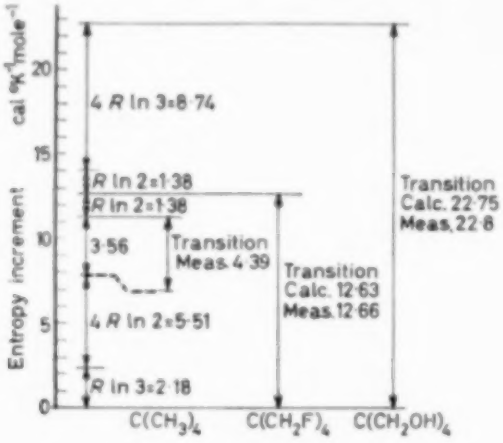


Figure 3. Entropy diagram

In addition to these factors, there are two orientational possibilities for the central $—CC_4—$ tetrahedron itself. Since one of the four-fold axes of this tetrahedron lies on a principal crystallographic axis of the cubic phase, the molecule as a whole may be rotated about this axis by 90°, effectively inverting the orientation of the $—CC_4—$ tetrahedron. Consequently, a term of $R \ln 2$ must be added for this effect. The total entropy calculated thus far for the transition in the fluoride is $6R \ln 2$.

In order to make further comparisons, it is necessary to consider the neopentane transition. The transition at 140°K as measured by Aston and Messerly[7] involves an increment of 4·39 e.u. The heat capacity does not change significantly upon transition, suggesting that there is no change in the molecular structure during the transition. Consequently, the 4·39 e.u. must arise from orientational possibilities, changes in crystal structure, and volume increment effects. If we are permitted to deduct arbitrarily 0·83 e.u. as a difference occasioned by the disparity in molecular size for the two latter effects, then the orientational part of this transformation amounts to 3·56 e.u. It is considered that the similarities between neopentane and

pentaerythrityl fluoride are great enough for the fluoride to exhibit all entropy terms found in neopentane in addition to the terms which may be calculated as due to the nature of the fluoride itself.

The total entropy change for the transition in the fluoride may, therefore, be considered to be the sum of the following entropy terms: 3·56 e.u. for the orientational part of the entropy increment occurring in the transition in neopentane; R ln2 for the orientation of the —CC_4— tetrahedron in the fluoride; 4 Rln2 for the orientations of the —CH_2F tetrahedra, and R ln2 for the introduction of the four fluorine atoms into the molecule. The total entropy was calculated from these terms to be 12·63 e.u., in excellent agreement with the measured value for the transition entropy of 12·66 e.u. occurring in the fluoride. This general situation is represented graphically in *Figure 3*.

At the present time measurements are being extended to higher temperatures to include the fusion thermal effects and provide an alternative basis for correlation.

Adamantane

Adamantane was prepared by the method of Schleyer[16]. The crystal structure was investigated by Giacomello and Illuminati[17] and by Nowacki[18]. At room temperature the structure is the face-centred cubic space group T_d^2–$F\bar{4}3m$. Further single-crystal X-ray diffractional studies on the forms above and below the transition temperature are at present being conducted in this department by Professor Christer Nordman and should aid significantly in the statistical interpretation of the data.

Note added in proof

Data and correlation devised subsequently to the oral presentation of this paper on these and related molecules are presented elswhere [19, 20].

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VOL
2
1961

PRE-FREEZING AND PRE-MELTING

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When attempts are made to interpret the solid–liquid transition in terms of molecular structure, highly significant information can emerge from phemomena of pre-melting and pre-freezing. Empirically, on approaching the transition between solid and liquid, characteristic parameters of the phase under examination may show an accelerated rate of change, in the sense of a premonition of the change due to take place at the transition point itself. It is convenient to consider separately thermodynamic parameters such as the heat content, the volume, and derived quantities, and rate process parameters which have included critical shear strength and diffusion for the solid, and viscosity and other transport parameters for the melt. In certain cases many other methods have become available in recent years, especially in studying pre-melting.

Depending on the nature of the crystal, thermodynamic phenomena of pre-melting may be very prominent, or almost imperceptible. Prominent examples with various crystal structures include heat content and volume changes in polymethylene compounds[1, 2], heat content change of lithium fluoride[3] and alkali metals[4], and thermal expansions of silver halides[5]. When only thermodynamic measurements are available, rigorous care is always necessary to eliminate a quite trivial effect known as " hetero-phase pre-melting ". This arises from a small mole fraction n/N of impurity when this is not soluble in the crystals but is soluble in the melt. Theory shows that the excess ΔQ of volume or heat content change, which arises from actual formation of small amounts of liquid at a temperature T below the limiting melting point T_f°, in such cases is related to the total change ΔQ° by the equation

$$\Delta Q^\circ/\Delta Q = N(T_f^\circ - T)/nK$$

where K is the cryoscopic constant.

By graphical integration, ΔQ can be evaluated from a plot of $\mathrm{d}\Delta Q/\mathrm{d}T$. This permits two direct tests of heterophase pre-melting; if this pre-dominates, a plot of $1/\Delta Q$ against T should give a straight line, and its slope N/n permits evaluation of the fraction of impurity causing heterophase pre-melting.

By these tests it is readily seen[6] that the marked pre-melting of potassium thiocyanate, for example, cannot be due to hetero-impurities, since these would have to be present to the extent of 3·5–7 per cent to account for the pre-melting observed, and furthermore do not yield a straight-line plot. It is significant that a plot of log ΔQ against $1/T$ gives a straight line for this salt, suggesting that its pre-melting is associated with homophase lattice defects obeying a law

$$n/N = C \exp - E/RT$$

Its slope with $E \simeq 58$ kcal/mole is suggestively near to the energy required to create lattice defects of about 47 kcal/mole, as estimated from conductance measurements on the solid. Quite apart from these calculations, after careful purification any likely impurities are retained in solid solution and have a homophase effect on pre-melting, through the lattice defects they introduce. Such impurities can even be added deliberately; small amounts hardly affect the curves obtained[1].

Another way of studying pre-melting where there is a marked change in heat content of the solid on approaching the melting point, is by precision cryoscopy. The solute added must not form solid solutions in the crystals. On progressive addition the freezing temperature falls, and the crystals separate with rapidly changing heat content; this becomes apparent by a changing cryoscopic constant. Tests on polymethylene hydrocarbons have been described by Oldham and Ubbelohde[7], and on potassium thiocyanate by Rhodes and Ubbelohde[8].

Non-thermodynamic techniques include ionic conductance and diffusion measurements on silver salts. Pre-melting effects run parallel with thermodynamic findings[5]. Optical measurements reveal pre-melting due to onset of rotation, for example in benzene[9–11]; dielectric measurements have been used to follow pre-melting in polymethylene ketones[12]. Ultra-violet absorption spectra confirm true homophase pre-melting of potassium thiocyanate[13]. Mechanical effects include a marked decrease in the plastic–elastic limit of cryolites on approaching their melting point, but theories underlying such effects have not yet attained sufficient confirmation to provide useful guides about structure.

All these premonitory changes in the solid state have no obvious explanation in terms of the classical Phase Rule concept of melting as a transition between completely independent solid and liquid phases. The changes resemble λ-point phenomena in solids, which have been given an interpretation in terms of " smearing " of the transformation and the co-existence of domains of alternative structure in hybrid crystals[14–16]. Related to this is an early theory about " heterophase fluctuations "[17]. However, two important considerations about melting make its relationship with a λ-point transformation only rather superficial:

(i) In all known cases, even when premonitory effects constitute a substantial fraction of the total change on passing from the solid well below the melting point, to the melt, there always is a discontinuous jump from solid to liquid at a melting point in properties such as the density. In other words, melting always is a discontinuous phase change, even if the two equations of state begin to approximate by a rapid change of slope before they actually intersect.

It seems possible that at sufficiently high pressures a continuous transition from solid to liquid might be attained. Theoretical arguments for and against a critical point for solid–liquid, by analogy with the well known critical point for solid–gas, have not yet reached finality[18]. The existence of marked pre-melting is an important consideration in such cases.

(ii) In ordinary λ-point phenomena, on both sides of the peak the crystals show long-range order; in the transition region the solid is a hybrid of domains of both kinds. However, since liquids do not show long-range

VOL. 2 1961

order, " heterophase fluctuations " involving a hybrid of solid and liquid offer no advantage as a model to explain pre-melting over the concept of " co-operative defects " in the crystals. For co-operative defects the energy of formation no longer remains independent of neighbouring defects, because their concentration is too large. For examples in relation to pre-melting see Oldham and Ubbelohde[7]; there are no doubt many other types.

When pre-melting is due to the onset of " rotation " of some kind in the crystal, as may be the case for many molecular crystals, suitable additives in solid solution can lower the potential barriers hindering this disorder and thus enhance the pre-melting. Tests on benzene crystals have been described by Thompson and Ubbelohde[19].

PRE-FREEZING IN MELTS

By analogy, the explanation of pre-melting as arising from co-operative defect formation in the crystals suggests that in liquids pre-freezing may involve incipient development of long-range order of some kind. Such incipient ordering of the molecules is conveniently described as " clustering ", and is likely to be favoured by certain molecular shapes, such as rods or plates. Most important is the fact that in pre-melting, the co-operative defects arise in a specific crystal structure. On the other hand, clustering of molecules in a melt can involve various alternative forms of incipient ordering. Usually no kinetic obstacles prevent all possible types of clustering from being realized simultaneously in the melt when the temperature is sufficiently low. On this model of a melt, pre-freezing involves increasing concentrations of the whole diversity of realizable clusters, dissolved in monomer. Transport properties of melts can give a sensitive indication of the presence of such clusters. For example, some polyphenyl molecules[20] such as *p*-terphenyl give melts with excellent straight-line polts of the relationship

$$\log \eta = A + B/T$$

where η is the viscosity.

Other closely related polyphenyl hydrocarbons such as *o*-terphenyl give evidence of very extensive cluster formation as the freezing point is approached and readily supercool to extremely viscous melts[21]. Extensive interlocking of the molecules into clusters accounts for the pre-freezing. When the liquid flows, these clusters behave like colloidal particles and the viscosity η can be written according to the Einstein formula

$$\eta/\eta_{s1} = 1 + 2{\cdot}5\Phi + 7\Phi^2 \ . \ . \ .$$

where η_{s1} is the hypothetical viscosity, calculated by extrapolation, which the liquid would have if it still consisted wholly of monomers, and Φ is the volume fraction of the melt occupied by the clusters[21]. *Figure 1* gives the fraction Φ for *o*-terphenyl calculated on this basis, from the experimental viscosity data.

Plots of specific volume of such melts against temperature show that the liquid supercools and readily passes into a glass. Since this evidence shows that spontaneous nucleation is practically absent in the supercooled melt,

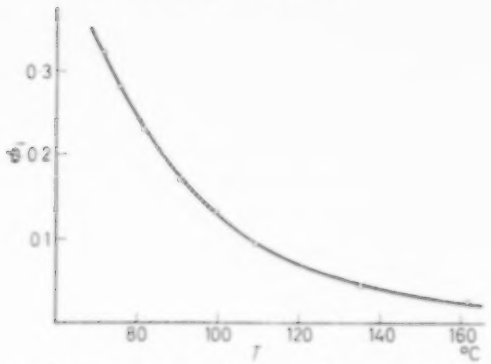

Figure 1. Cluster formation in *o*-terphenyl[21]. (*By courtesy of the Faraday Society*)

practically none of these clusters can have the structure of crystal nuclei capable of giving long-range order in three dimensions. This can be readily understood in the light of the well-known theory of Volmer, Becker and Doring about the concentration of crystal nuclei in a melt, provided allowance is made for the fact that there can be many alternative forms of cluster packing which are incapable of indefinite extension in three dimensions. Even with simpler quasi-spherical molecules, non-crescible modes of cluster-packing can be important in the melts as the freezing points are approached (cf. Frank, references in Ubbelohde[14–16]).

Though transport properties other than the viscosity can be likewise sensitive to cluster formation, they have been much less investigated; the thermal conductivity of some *n*-polymethylene hydrocarbons indicates marked pre-freezing phenomena (*Figure 2*).

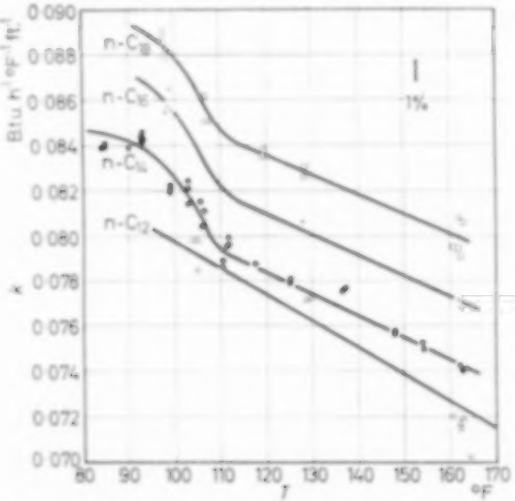

Figure 2. Thermal conductivity of some n-polymethylene hydrocarbons. (*By courtesy of the American Institute of Chemical Engineers*)

VOL. 2 1961

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VOL.
2
1961

THE MELTING MECHANISM OF THE ALKALI THIOCYANATES

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INTRODUCTION

The melting of a solid always implies a transition from a state of comparatively high order to one of comparative disorder. A measure of the increase of disorder or randomization on melting is given by the Boltzmann relationship

$$S_f = R \ln W_L/W_s,$$

where W_s and W_L represent the number of independent ways of realizing the arrangements of solid and melt respectively and S_f is the entropy of fusion. Each new kind of disorder which occurs on passing from the crystal to the melt involves a new mechanism of randomization on melting. Ubbelohde[1] has summarized the different ways of randomization in the transition from the solid to the melt as positional, orientational, vibrational and configurational randomization. Other terms, which in certain cases can make large contributions to the entropy of fusion, are those due to the presence of mesomorphic states and the formation of association complexes in the melt[2]. Treating these increases of disorder as independent and additive, S_f becomes to a first approximation:

$$S_f = S_{\text{positional}} + S_{\text{orientational}} + S_{\text{vibrational}} + S_{\text{configurational}} + S_{\text{association}} + \ldots .$$

Generally, in an ideal case the melting point is sharp and it is assumed that the free-energy curves for the liquid and solid phases are completely independent. In certain cases, however, this is not strictly true and there are changes in slope of the free energy curve of the solid state before the two curves intersect[3]. This phenomenon is known as "homophase premelting" and occurs whenever the structures of the two phases are very similar (e.g. the crystalline paraffins)[2].

This paper is concerned with the melting mechanism of the alkali thiocyanates which are a group of low melting ionic salts such as:

LiSCN, m.p. 237°C; NaSCN, m.p. 305°C; KSCN, m.p. 177°C; RbSCN, m.p. 195°C

The following sections review the available experimental evidence with regard to the melting mechanism of these salts and a theory is put forward to account for their very low melting points.

THERMODYNAMIC PARAMETERS

The potassium salt is the most stable of the alkali thiocyanates, decomposition starting at approximately 250°C in the melt. Lithium thiocyanate decomposes on heating in the solid state and sodium thiocyanate decomposes on melting. *Table 1* compares the melting points, entropies, heats of fusion and volume changes for the sodium and potassium thiocyanates, nitrates and chlorides. The entropies of fusion of all these salts are approximately the same, but the latent heats of fusion (H_f) of the salts with spherically symmetrical anions (halides) are nearly twice as large as those for the salts with the irregularly shaped anions (nitrates and thiocyanates). The increase in the heat content of a salt on fusion is primarily due to the increased randomness of motion of its constituents (i.e. positional randomization) which depends on the volume increase on fusion.

Table 1. Thermodynamic parameters

Salt	*Ref.*	T_f (°C)	H_f (kcal/mole)	S_f (e.u.)	$\Delta V_f/V_s$ (%)
NaCl	4	800	7·20	6·7	30·0
KCl	4	769	6·42	6·16	23·0
$NaNO_3$	4	308	3·85	6·63	11·0
KNO_3	4	333	2·57	4·25	—
NaSCN	5	310	—	—	7·2
KSCN	5	177	3·39	7·56	5·4

The alkali halides show large volume changes on fusion, whereas for the other salts the volume change is small. Since T_f (the temperature of fusion) is also small, particularly for potassium thiocyanate, and $T_f = H_f/S_f$ there must be additional modes of entropy uptake for potassium thiocyanate on melting, other than that caused purely by positional randomization. The

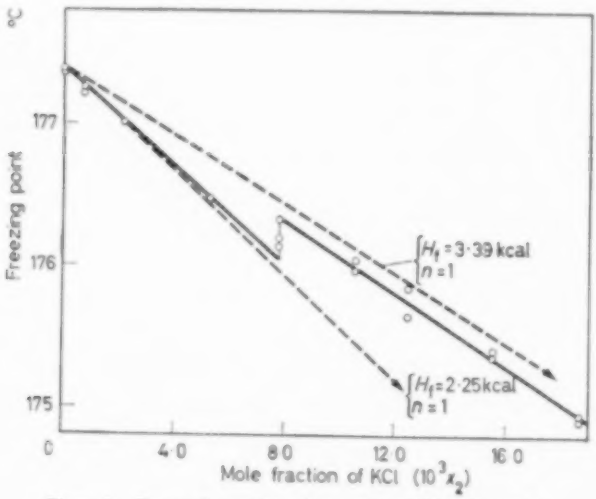

Figure 1. Depressions of freezing point of KSCN by KCl

VOL. 2 1961

dilational changes with temperature for potassium thiocyanate are of great interest[5]. These indicate that marked homophase pre-melting occurs in this compound. The small overall change in volume on melting suggests a randomization mechanism which involves the rearrangement of a proportion of the ions into association complexes in the melt which do not require a large increase in volume.

A literature search also revealed that there were marked discrepancies in the values of H_f determined cryoscopically and calorimetrically[6]. Recent research in these laboratories has been directed to evaluating, by precision cryoscopic methods, the latent heat of fusion of potassium thiocyanate[6]. The results shown (*Figure 1*) can be interpreted if there is a transition in this salt in the immediate neighbourhood of the melting point. The dilatometric results suggest that this transformation is continuous, and that it occurs in the previously observed pre-melting region.

TRANSPORT PROPERTIES

Viscosity and conductivity measurements in molten potassium and sodium thiocyanates indicate that the transport properties of these salts are anomalous when compared with those for the alkali halides.

Table 2. Migration parameters of melts[5]

Salt	$10^3\ \sigma_1/T_f$	E_η (kcal/mole)	E_σ (kcal/mole)	E_η/E_σ
NaCl	3·30	9·40	1·54	6·11
KCl	2·04	7·83	2·30	3·40
NaSCN	1·15	4·70	4·74	0·99
KSCN	0·34	5·72	5·85	0·98
$NaNO_3$	1·69	3·85	2·02	1·91
KNO_3	1·05	4·41	2·85	1·55
$KHSO_4$	0·10	11·95	6·2	1·93

Table 2 shows that the ratio σ_1/T_f (σ_1 is the conductivity of the melt just above the melting point) is much smaller for the low-melting salts. This, again, is evidence in favour of the formation of association complexes in molten thiocyanates. Also, at temperatures considerably above the melting point the ratio E_η/E_σ (E_η = energy of activation for viscous flow; E_σ energy of activation for conduction in the melt) approaches unity for the low melters. This can be explained if E_σ refers to large clusters of ions, such as occur in associated melts. Plester *et al.*[5] also found that E_η is greater for potassium thiocyanate at temperatures close to the melting point than at higher temperatures. On the other hand, E_η for potassium chloride remains contant. If association complexes do occur in the melt one would expect a greater number near the freezing point, which would explain the higher initial value of E_η.

In transport measurements in the solid phase, there is a complex temperature dependence. A plot shows the usual upper and lower slopes for the curve with changes at the crystal transition temperature (142°C). Near the freezing point there is a steep rise in conductivity which corresponds to the pre-melting region found in volume measurements[5].

CRYSTALLOGRAPHIC AND OPTICAL PROPERTIES

The crystallography of the thiocyanates is rather complex[7], but it can be assumed that the SCN^- ion is linear with the following bond distances[8]: S—C 1·61Å and C—N 1·17Å. Klug has evaluated the crystal structure of potassium thiocyanate at 25°C; the SCN^- ions lie in parallel planes[9]. In view of the reported volume changes and crystal transition at 142°C for this salt, the high-temperature crystal structure is probably different; however, it is most likely to be one of increased symmetry.

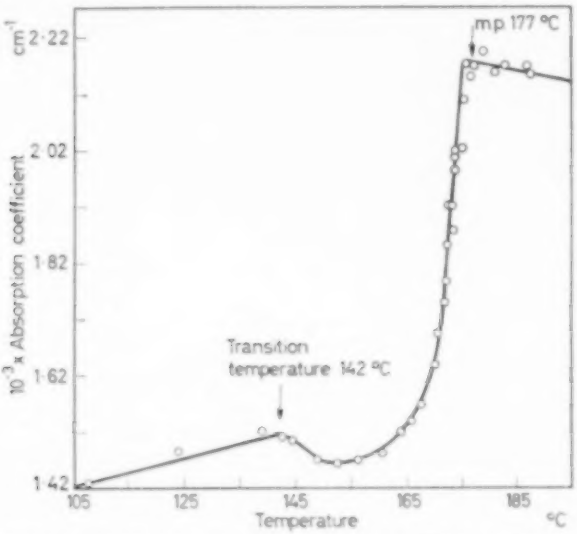

Figure 2. Ultra-violet absorption coefficient of KSCN at 2300Å

Recently the melting transition of potassium thiocyanate has been studied by ultra-violet absorption spectroscopy, which provides a means of studying environmental changes with temperature[10]. Both E_{max} and absorption coefficient curves (*Figure 2*) confirm homophase pre-melting for this salt, since marked changes in these parameters are observed before the melting point is reached. Evidence for the formation of association complexes in molten potassium thiocyanate is given by the marked rise in the value of the maximum absorption coefficient, compared with that found for salts which show simple positional randomization on melting (*e.g.* LiI).

PROPOSED MELTING MECHANISM OF THE ALKALI THIOCYANATES

The evidence so far available indicates that a number of modes of randomization are available when the alkali thiocyanates melt.

As in all ionic salts, positional randomization of the constituent ions is important for potassium thiocyanate, and orientational randomization also plays a part. However, it is unlikely that orientational randomization for SCN^- is complete, since the volume increase on fusion is too small to permit

VOL. 2 1961

free rotation. Viscosity, conductivity and spectroscopic measurements all point to the existence of association complexes or ion-pairs in the melt. The formation of association complexes would add a considerable term to the entropy of fusion without materially affecting the heat of fusion. This is confirmed by the low latent heat of fusion of potassium thiocyanate. The thiocyanates, in particular the potassium salt, show large pre-melting effects in the solid immediately below the melting point. This suggests that there is extensive formation of co-operative flaws in the crystalline state[11]. Such extensive flaw formation would tend to increase the disorder of the solid state, leading to a higher energy content for the solid close to the melting point, which will eventually result in a smaller heat of fusion. The apparent crystal transition found in the cryoscopic measurements also indicates that the solid state is very disordered close to the melting point.

Summarizing, it may be said that positional and orientational randomization occur on melting the thiocyanates and that there are also important contributions from the formation of association complexes in the melt and pre-melting in the solid.

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VOL
2
1961

NUCLEATION STUDIES ON IONIC MELTS

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INTRODUCTION

Previous work on crystal nucleation in one-component melts has largely been confined to molecular liquids or metals. Molecular liquids have been studied in bulk[1], and in the form of clouds of droplets produced by condensation in supersaturated vapour[2–6]. Metals have also been studied in bulk[7, 8], and as droplets of microscopic size. These were produced either singly by melting small fragments[9, 10], or in large numbers in emulsions[11, 12]. For some purposes it is an advantage, in studying supercooling, to subdivide a sample of melt into a large number of droplets, thereby reducing to a small fraction the number which might contain impurities. In particular, only droplets free from impurities may be relied upon to exhibit phenomena of spontaneous nucleation.

Apart from work on glasses, where crystallization is very slow, little information exists on the spontaneous nucleation of ionic melts. In spite of experimental difficulties due to their high melting points, work on inorganic salts containing simple ions seems likely to prove rewarding, especially in view of the additive properties of the inter-ionic forces. Central, Coulombic force fields are more amenable to theoretical treatment than those in other classes of compounds, as is evident from the considerable success with which they have been used to predict the lattice energies of ionic solids.

A short description is given below of a new technique for studying the solidification of molten salts at high temperatures, together with some preliminary results obtained with alkali halides.

EXPERIMENTAL

Experiments with ionic salts are in progress in this laboratory, using a furnace in which clouds of melt droplets are formed in an atmosphere of salt vapour by intermittent supersaturation. Condensation is induced in an inert supporting gas by raising the temperature of a salt bead above that of the surroundings for a short interval, usually about 0·5 sec. The bead is supported on a small platinum heater coil in the roof of a chamber in the carbon furnace-lining. The chamber takes the form of a horizontal cylinder loosely closed at its ends with windows of transparent silica. Thermocouples embedded in the walls are used to measure the temperature of the gas in the enclosure. The movement of condensed particles by sedimentation and convection can be controlled by judicious use of the supersaturator so that they may be made to grow or evaporate at will while circulating slowly in the supporting gas. The cloud is illuminated by a mercury arc lamp placed opposite one end of the furnace, and the

forward-scattered light is viewed with a telescope at the other end. In this way the light reflected from single droplets can be studied, and their solidification detected by the onset of " twinkling ", described below.

The present method, in which light scattered from discrete particles can be observed, has certain advantages over previous techniques[2–4], in which the appearance of the illuminated cloud was examined by the unaided eye. Some doubt exists[14] as to whether failure to observe scintillations in these earlier experiments was a reliable indication of the absence of solid particles. Care is necessary, however, even where variations in the intensity of forward-scattered light can be detected. Thus it has been observed in the present work that dense clouds of droplets under strong illumination show an effect which resembles the twinkling of crystals. This is due to the fact that neighbouring droplets move through critical positions in which light scattered from one reinforces that from the other. A droplet passing through several of these positions is thus seen to twinkle. This effect is nevertheless easily distinguishable from the behaviour of solid, since twinkling of droplets dies away as the cloud disperses, whereas crystals twinkle as they slowly rotate in the gas, even when isolated.

The aim of the present experiments is to measure the maximum supercooling in clouds of various compounds by observing the temperature at which solidification is complete in a convenient interval of time. The choice of this interval is limited by the period for which individual droplets can be identified, and is usually about 10 sec. Before recording the behaviour of droplets at a given temperature any catalyst impurities are removed from the supporting gas by one or two preliminary condensations. Several successive clouds are then examined to ascertain the reproducibility of results.

In all experiments carried out so far it has been possible to measure only the temperature corresponding to the sudden onset of crystallization. The rate of freezing turns out to be so sensitive to temperature that once it becomes detectable at all, the whole cloud solidifies in the observation period. This kind of behaviour is quite a general experience in nucleation studies and provides support for the predictions of theory, while at the same time severely limiting its practical investigation.

The apparently uniform frequency and intensity of twinkles from solidified droplets suggests that they are, in fact, tiny cubes rotating at about one revolution per second. Their rate of fall in the stationary gas indicates a particle size in the range 1–5 microns. Microscopic examination of the fall-out from condensations in various alkali halide vapours confirms this and also shows that the crystals are of roughly cubic form. It seems likely, moreover, that the particles are single crystals since an electron diffraction study by Young and Morrison[15] of sodium chloride particles prepared by condensation of vapour showed that these were monocrystalline with a normal lattice parameter.

It has also been observed that particles at the threshold of solidification do not twinkle immediately on formation, delays of up to several seconds being typical. As practical limits to the range of observable twinkling frequencies are set on the one hand by the persistence of vision and on the other by the observation time, it would be possible in the absence of

further evidence to attribute the lack of twinkling either to very slow or to very fast rotation. However, calculations of the influence of particle size on rotation frequency, based upon the exchange of energy between the rotational inertia of the particle and the Brownian motion of the gas molecules, show that twinkling of crystals should be detectable for all particles visible with the present method. Furthermore, a stroboscopic technique, in which the early stages of drop life were examined in a periodically interrupted light beam, failed to produce evidence of rapid twinkling. It therefore seems that twinkling is a reliable indication of the presence of crystals, and that in the early stages of their existence particles at the threshold temperature are partly or wholly liquid.

In addition to the onset of twinkling, further indications of the freezing of droplets are provided by changes in the rates of growth and evaporation. Whereas, for example, a large proportion of liquid droplets may evaporate entirely during the period of observation, especially at temperatures above the freezing threshold, twinkling particles are lost mainly through sedimentation. This behaviour forms the basis of a useful method for roughly locating the critical temperature of solidification, since at slightly higher temperatures the drop size changes so rapidly that the period of observation is materially shortened by distillation and fall-out.

The observed difference in growth rates of liquid and solid particles is not entirely attributable to the higher vapour pressure of the liquid. Droplets probably have an accommodation coefficient approaching unity, but this is not necessarily true for solid particles. The probable monocrystalline nature and cubic habit of the crystals obtained in the present experiments suggests that the predominant growth mechanism is one involving two-dimensional nucleation. Further growth of a crystal, once it has been formed by the solidification of a droplet, therefore depends on the maintenance of marked vapour supersaturation.

RESULTS

Some preliminary results for alkali halides are given in *Table 1*. In columns 2, 3 and 4 are listed the melting points T_f, the nucleation threshold T_n, and the critical supercooling θ. Salts of " analytical reagent " grade were normally used, without further drying or other purification. The supporting gas was usually argon, although its replacement by nitrogen made no measurable difference to the results for potassium iodide. Saturation of the argon at room temperature with moisture had no effect

Table 1. Data for homogeneous nucleation in molten alkali halides

Salt	$T_f^{(20)}$ (°K)	T_n (°K)	θ (°K)	$\sigma_{[001]}$ (erg/cm²)	γ (dyne/cm)	λ^*/d	N^*
NaF	1265	985	(280)	252	230·4	8·9	700
NaCl	1074	911	163	102	125·7	8·8	680
NaBr	1023	862	161	85·5	117·6	9·0	740
KCl	1045	877	168	78·5	109·5	9·1	750
KBr	1013	850	163	69·5	100·2	9·1	750
KI	958	804	154	57·0	88·2	9·1	750
RbCl	988	845	143	51·8	110·6	9·9	980

on the critical supercooling of potassium iodide, neither was this influenced by using a supersaturator bead containing about 10 per cent of potassium hydroxide. Material obtained from large monocrystals of sodium chloride and potassium bromide, of the quality used in the manufacture of prisms for infra-red spectrometers, gave results which were indistinguishable from those obtained with commercial reagents. It is concluded that partial hydrolysis does not significantly affect the nucleation mechanism for these salts. Insensitivity to impurities has also been observed by Staveley[2, 3] in nucleation experiments with various molecular compounds. Some difficulty was experienced with sodium fluoride in inducing condensed particles to grow to appreciable size. This may have been connected with the fact that clouds were noticeably polydisperse in this case. Also the onset of twinkling was less distinct for sodium fluoride.

DISCUSSION

The critical supercoolings recorded in *Table 1* are quite large, that for sodium fluoride being especially so, although there is reason to believe that for this salt the recorded result is somewhat too high (see below).

The interpretation of critical supercoolings in terms of the theory of homogeneous nucleation involves certain assumptions. The first and most important of these is to regard the formation of a three-dimensional crystal nucleus within a droplet of liquid as the rate-controlling factor in the solidification process. This enables one to identify the temperature of sudden freezing with the threshold of nucleation. The observations of Turnbull and Cech[10] on the freezing of metal drops indicated that this was plausible, and further support is provided by our own observations with alkali halides. Formation of single crystals in our experiments suggests growth from single three-dimensional nuclei, and it follows that the growth rate in the liquid greatly exceeds the rate of nucleation at the temperatures concerned.

A basic postulate of the more recent theories is that the observed nucleation rate is governed by a stationary distribution of embryos of all sizes up to and including that of the critical nucleus itself[16, 17]. Approximate theoretical estimates for the condensation of vapours[18, 19] indicate steady-state relaxation times of 10^{-5} or 10^{-6} sec. Growth and decay of embryos in condensed systems are, however, activated processes and associated relaxation times may be much longer[19]. Calculations show that under the conditions of the present experiments droplets can cool by radiative heat loss through several hundred degrees to the end temperature (the furnace temperature) in a few milliseconds. For relaxation times appreciably longer than this, therefore, it is the furnace temperature which governs the rate-determining process of nucleation.

The stationary embryo distribution specified by theory might not, in fact, be entirely realized in the present type of experiment, since the rapid solidification of a droplet could terminate the relaxation process as soon as a critical nucleus appears. In applying the theory it is therefore necessary to assume that the first effective nucleus forms at a late stage in the relaxation process. Some justification for this assumption is provided by the results of the calculations now described.

VOL. 2 1961

Using the supercooling data of *Table 1* critical free energies of nucleation ΔG^* were calculated from the expression of Turnbull and Fisher[17] for the rate I of homogeneous nucleation in pure liquids. This may be written

$$I = (kT/h)(V/v_m) \exp(-\epsilon/kT) \exp(-\Delta G^*/kT) \text{ sec}^{-1} \quad (1)$$

where V is the volume of liquid, v_m the volume per molecule in the liquid, and ϵ an activation energy for the assimilation of liquid molecules by the growing embryos. A value of 0·1 sec^{-1} was assigned to I at the nucleation threshold. As there appear to be no data on the activation energy for viscous flow in supercooled alkali halide melts, which is the parameter usually employed for ϵ, a middle value of 10 kcal/mole was chosen after considering viscosity data for the salts above their melting points[22, 23]. This seems justifiable since for uni-univalent salts ϵ is not very sensitive to temperature. Moreover, values of the liquid–solid interfacial free energy σ, calculated from ΔG^*, are insensitive to ϵ. The liquid volume V was taken as 10^{-11} cm^3, corresponding to a droplet diameter of 3 μ. A cubic nucleus was assumed and $\sigma_{[001]}$ was obtained from[24]

$$\Delta G^* = 32\ \sigma_{[001]}^3 (v_m/\Delta g)^2 \quad (2)$$

where Δg is the difference in free energy per molecule between the bulk liquid and solid phases. An approximate value for this quantity is obtained from the expression

$$\Delta g = \Delta H_f \theta/(T_f N) \quad (3)$$

where ΔH_f is the molar heat of fusion and N is the Avogadro number. Equation (3) is deduced by assuming that the heat content and entropy changes at T_n are equal to those at the melting temperature.

Where the necessary heat capacity data are available enthalpy changes may be corrected to T_n, and Δg calculated from

$$\Delta g = (\Delta H_f/T_f - \Delta C_p)\,\theta/N \quad (4)$$

In view of the shortage of data[18], reliable corrections can only be made for some of the salts studied. The values given in the table for $\sigma_{[001]}$ were calculated using equations (2) and (3), and may be as much as 10–20 per cent too high.

With these reservations, the resulting interfacial free energy σ may be compared with the surface tension γ of any melt at its nucleation temperature. The values of γ listed in *Table 1* were obtained by extrapolating the curves of Jaeger[21] to T_n. On the view that the free energy of an interface is a measure of the extent of structural change across it, it is to be expected that γ will exceed σ. Results in *Table 1* show that this is indeed the case for all the compounds examined excepting sodium fluoride. Heat capacity corrections using equation (4) in place of equation (3) would probably remove this discrepancy. It is also possible, as stated above, that the supercooling for this compound has been over-estimated.

Also tabulated are values for the ratio of the length λ^* of an edge of a critical nucleus to the distance d between nearest-neighbour ions in the crystal. λ^* was calculated from the thermodynamic expression for a cubic nucleus[24]:

$$\lambda^* = 4\,\sigma_{[001]}\,v_m/\Delta g \qquad (5)$$

both equations (2) and (5) being derived on the assumption that edge and corner free energies are negligible in comparison with the total interfacial free energy.

Although the values obtained for λ^*/d are plausible it must be emphasized that they merely illustrate the order of nuclear size, since the assumption that the nuclei are cubic may not be justified.

The same objection does not apply to the values in the final column of the table, which refer to the total number N^* of ions in the critical nucleus. This is given by

$$N^* = 4\,\Delta G^*/\Delta g \qquad (6)$$

and is calculated using equations (1) and (3). Some restriction on nuclear shape is involved in calculating N^*, however, since equation (6) is derived by assuming that σ is uniform over the whole surface of the growing embryo. Values of N^* so calculated are also subject to inaccuracies in Δg, and it is estimated that for this reason absolute values of the tabulated results may be too low by as much as 30 per cent. Nevertheless, relatively, the sizes of nuclei are the same to within an order of magnitude for all the salts studied. A mean radius of about 25 Å is indicated.

At present, the only other evidence about the structure and size of nuclei in ionic melts stems from X-ray studies by Zarzycki[25]. This author suggests that in alkali halide melts at temperatures slightly above the melting points there are regions about 8 Å across in which the order is much the same as in the crystal. However this may be, present findings indicate that to be effective in producing observable crystallization rates, nuclei for alkali halide melts must be considerably larger.

Direct calculations of the free energy of nucleation from first principles would be very useful as a check on the experimental findings, but for the large sizes of nuclei now found such calculations are not at present practicable.

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VOL. 2 1961

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VOL.
2
1961

IONIC AND MOLECULAR ROTATION IN AMMONIUM SALTS AND CLATHRATE COMPOUNDS

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It was at one time rather widely believed that certain ions and molecules could rotate virtually freely in the lattice containing them. It now appears that such almost free rotation, in the literal sense, is probably rare. The solids which have been most thoroughly investigated are ammonium chloride, bromide, and iodide. It has been established beyond doubt that in the simple cubic forms of these salts the ammonium ions do not rotate, being prevented from doing so by energy barriers of 6410, 4645 and 4100 cal/g-ion, respectively[1]. It is to be noted, however, that there is a considerable decrease in this energy barrier as the lattice dimensions increase, and the possibility must still be considered that in ammonium salts where the anion is large, symmetrical, and not too highly charged, the barrier is small enough for the ammonium ion to undergo something approaching free rotation at room temperature. Another circumstance which will be favourable to free rotation is if the disposition of the anions about the ammonium ion is such as to give only a slight energetic preference for one orientation rather than another. This happens, for example, in the high-temperature face-centred cubic form of ammonium iodide, where the tetrahedral cation is surrounded octahedrally by six anions. Each ammonium ion directs one N—H bond towards one of the anions. The barrier to one-dimensional rotation about this bond is, however, then so small (< 100 cal/g-ion) that the ammonium ions must at room temperature undergo almost free rotation about one N—H bond[2].

With these considerations in mind we have studied the motion of the ammonium ion in several selected ammonium salts by attempting to estimate the contribution made to the heat capacity C_p of the salts by the rotational or torsional movements of the ammonium ions. All the salts investigated have isomorphous rubidium salts, and the lattice dimensions of the ammonium and rubidium salts differ by less than 1 per cent. It is therefore reasonable to suppose that, for a given pair of such salts, the quantity $(C_p - C_v)$ and the contribution to C_p from the torsional oscillations of the *anion* will be almost equal. Consequently, at temperatures high enough for the lattice vibrations to make effectively their maximum and hence identical contributions to C_p, the quantity $\Delta C_p = C_{p,\mathrm{NH_4\ salt}} - C_{p,\mathrm{Rb\ salt}} - C_{\mathrm{int}}$ should give the contribution made by the torsional oscillations (or rotations) of the ammonium ions (C_{int} is the relatively small contribution from the internal vibrations of the ammonium ion). We may distinguish, for convenience, between three possibilities for ΔC_p (expressed per g-ion) as a function of temperature.

(1) If the barrier to rotation is sufficiently high, ΔC_p will rise to a limiting value of $3R$. This may not be reached at room temperature. An example of this is given by ammonium chloride, in which the torsional oscillation frequency of the ammonium ion is high (360 cm^{-1}) and ΔC_p at 25°C is still only $\sim$ 4·7 cal $°C^{-1}$ g-ion^{-1}.

(2) If the barrier is so small that the ammonium ions virtually rotate freely, ΔC_p will be $\frac{3}{2}R$.

(3) With barriers of intermediate height, the ammonium ions will behave as restricted rotators, and with rising temperature ΔC_p will rise to a maximum and then decrease, approaching $\frac{3}{2}R$ asymptotically.

So far in this laboratory, the following salts have been investigated by this comparative method: ammonium tetraphenylboron[3], $NH_4B(C_6H_5)_4$; ammonium stannichloride, $(NH_4)_2SnCl_6$; ammonium stannibromide[4], $(NH_4)_2\ SnBr_6$.

ΔC_p for ammonium tetraphenylboron provides another example of case (1) above. At room temperature, ΔC_p is only $\sim$ 5cal $°C^{-1}$ g-ion^{-1} and still rising. So, in spite of the large size of the anions the ammonium ions do not even approach free rotation. A crystallographic study of this salt[5] showed that the tetraphenylboron ions are arranged in parallel columns, with an ammonium ion trapped between two neighbouring anions in one and the same column. The unoccupied space in the lattice is chiefly that between the columns and is therefore not available to the ammonium ions. On the other hand ΔC_p for ammonium stannichloride rises to a maximum of 4·8 cal $°C^{-1}$ g-ion^{-1} at 180°K and by 25°C has declined to a value of 4·1 cal $°C^{-1}$ g-ion^{-1}, which is roughly half-way between the extreme values of $3R$ and $\frac{3}{2}R$. For the stannibromide the position is much the same; at 25°C, ΔC_p is 4·3 cal $°C^{-1}$ g-ion^{-1} and is decreasing. The ammonium ion in these two salts therefore behaves as a restricted rotator (case (3)). Ammonium stannichloride and stannibromide both have antifluorite structures. Each octant of the unit cell has an ammonium ion at its centre which is surrounded by four stannihalide ions. The tin–halogen bonds lie along or parallel to the axes of the unit cell, and each ammonium ion is surrounded by four tin atoms and by twelve equidistant halogen atoms. Although the height of the energy barrier restricting free rotation cannot be precisely estimated from the ΔC_p values, it must be considerably less than in the ammonium halides in their simple cubic forms. From quantitative considerations of the interaction between the ammonium ion and the neighbouring stannihalide ions it appears that this can only be so if the charge distribution in the stannihalide ion does not differ very much from zero charge on the tin atom and an effective charge of $-\frac{1}{3}$ located at the centre of each halogen atom. It is worth noting that if, by refining the analysis of C_p, it becomes possible to make reasonably reliable estimates of the potential barrier restricting ammonium ion rotation in salts with complex anions, then with the aid of sufficiently accurate crystallographic data it should be possible to draw conclusions about the charge distribution within the complex ion, since that within the ammonium ion is already known from Hornig's work[6].

The discovery of clathrates (or inclusion compounds) has made it possible to study the behaviour of small isolated molecules trapped in cavities in

VOL. 2 1961

lattices of almost fixed size. The best known clathrates are those formed by quinol. This substance can crystallize in an unstable β-modification, in which there are approximately spherical cavities regularly dispersed throughout the lattice. There is one cavity to three quinol molecules. By producing the β-form in the presence of a given kind of small molecule, e.g. by carrying out the crystallization in the presence of, say, argon under pressure, the resultant crystals contain small molecules trapped individually in the cavities. The proportion of holes filled can vary from a few per cent to almost 100 per cent in favourable cases, and the molecules which can be so trapped include those of argon, krypton and xenon, numerous diatomic molecules, methane, sulphur dioxide, and even molecules as large as methyl alcohol and acetonitrile. In a sense, clathrates provide idealized examples of the cell model which has played such a large part in recent theories of pure liquids and solutions, and it is therefore of interest to investigate the motion of the small molecules in the cavities. We have recently made such a study of the methane clathrates by measuring the contribution made to C_p per mole of methane. In principle this can be done by measuring C_p for any one clathrate of known composition and also for the pure β-quinol itself, but although this can be prepared, it is rather unstable and it is better to make measurements on two or preferably more samples of different composition. In order to decide whether the methane molecules are rotating within the cavities, it is necessary to assess C_{vib}, the contribution made to the heat capacity by the vibrational or translational movement (the " rattling ", as it were) within the cavity. This may be done with the help of a statistical theory of clathrates due to J. H. van der Waals[7] (which uses the cell model approach of Lennard-Jones and Devonshire), which enables C_{vib} to be calculated using, *inter alia*, data on the intermolecular potential energy parameters for pairs of the small molecules. To check the reliability of the C_{vib} values calculated in this way, we have made a careful study of the argon clathrates, where the whole of the contribution of the argon molecules to C_p is of course C_{vib}, and we find reasonably good agreement between the observed and calculated values[8]. An analysis of the results for the methane clathrates on this basis shows that the contribution to be attributed to the rotational or torsional motion of the molecules is from ~ 150°K upwards constant at $\frac{3}{2}R$ within 0·3 cal °C^{-1} mole^{-1}, thus leaving no doubt that in this range these molecules rotate virtually as freely as gaseous molecules. Only an approximate analysis of the heat capacity can be made at lower temperatures, since the treatment of J. H. van der Waals then no longer applies, but it seems that the course taken by the rotational heat capacity of the methane molecules does not differ much from that calculated for gaseous methane.

A similar conclusion has been reached in a different way about the oxygen clathrates by Meyer, O'Brien and Van Vleck[9], who, from a study of the magnetic properties of the clathrate at low temperatures concluded that rotation of the oxygen molecule is impeded by a barrier of only 127 cal/mole of O_2, so that here again at higher temperatures the rotation will be virtually free. It may therefore be expected that this situation prevails with several clathrates with sufficiently small molecules. On the other hand, it is known that the inclusion of larger molecules such as acetonitrile and methyl alcohol appreciably changes the lattice dimensions of the β-quinol and therefore

deforms the hole, so that it may be doubted whether these molecules can undergo free rotation within the cavities, at least in all their degrees of freedom.

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VOL.
2
1961

THERMODYNAMIC PROPERTIES OF POLAR SUBSTANCES: ENTHALPY OF HYDROCARBON–ALCOHOL SYSTEMS

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The industrial interest in petroleum compounds has generated large amounts of data for both pure components and mixtures of hydrocarbons. These data and the general similarity in molecular structure of the components have made it possible to develop reasonably precise methods for predicting thermodynamic properties of hydrocarbons over a wide range of conditions. When chemically dissimilar mixtures are encountered, much larger deviations from ideal behaviour are observed. Further, data for these systems are meagre. As a result, adequate prediction methods have not appeared for such systems. This paper presents: (1) a method of correlating data for strongly polar substances, such as alcohols in the pure state and when mixed with hydrocarbons, and (2) experimental enthalpy data for the binaries and pure components in the systems benzene–ethanol and n-pentane–ethanol.

Enthalpy data for non-polar–polar mixtures over a range of temperatures and pressure are generally not available. McCracken and Smith[9] have reported measurements on binary mixtures of benzene–methanol over extended ranges of temperature and pressure. They proposed a correlating procedure based upon association of the methanol. Data for one composition of a ternary system, n-hexane–benzene–methanol were also reported.

SCOPE OF INVESTIGATION

Enthalpies were measured for pure ethanol, benzene and n-pentane, and binary mixtures containing 25, 50 and 75 mole per cent ethanol in benzene and n-pentane. These data covered a temperature range of 250° to 500°F at pressures from 50 to 1700 p.s.i. Additional experimental information was obtained in the critical region. In addition, the effect of pressure on the enthalpy of n-propanol was computed from the volumetric data of Ramsey and Young[10].

Heat-of-mixing data of the liquids were used in order to place all mixture enthalpies on the same basis: pure liquid components at 77°F and their individual vapour pressures. The heats of mixing of Schnaible *et al.*[11] were used for the benzene–ethanol system. Measured values for the n-pentane–ethanol system were not available, but were estimated to be: 7·8, 9·4, and 8·7 B.t.u./lb. of mixture at 25°C for the 75, 50, and 25 mole per cent ethanol mixtures, respectively.

The experimental results covered both liquid and vapour regions. To understand more about the behaviour of polar substances, the vapour data

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only were analysed in an attempt to develop prediction procedures for the enthalpy of pure alcohols and their binary mixtures with hydrocarbons. The methods propose a means of evaluating the deviations from ideal gas behaviour.

EXPERIMENTAL

The experimental method was the same as used by McCracken and Smith[9]. This involves the measurement of the energy transferred from the mixture flowing through a calorimeter to boiling " Freon 11 ". The enthalpy change between the states at the inlet and the outlet to the calorimeter could be calculated from the weight of " Freon " evaporated and its latent heat of vaporization. The mixture leaving the calorimeter was always cooled to a temperature within 2°F of the boiling point of the " Freon ", 74°F. The exit stream was liquid at this temperature for all of the mixtures investigated.

RESULTS

The steady-state energy balance across the calorimeter, neglecting kinetic and potential energy changes, gives the following expression for the change in enthalpy of the fluid stream,

$$\Delta H_c = \frac{-L_f W_f}{W_m} \tag{1}$$

Correction must be made to the ΔH_c values obtained from equation (1) to refer the enthalpies to the desired standard state.

Operation of the equipment was most convenient when the inlet temperature was held constant and the pressure varied as each sample was taken. Each series of runs at constant temperature establishes an isotherm on a pressure–enthalpy diagram. The intersection of the three distinct curves obtained below the critical temperature represented points on the phase envelope. A series of isotherms would then define the phase envelope for the mixture. Additional data were taken in the critical region at constant pressure at close temperature intervals. These data were used to define more accurately the critical region on the temperature–enthalpy diagrams.

PREDICTION OF ENTHALPY OF PURE COMPONENTS

The equation proposed for the enthalpy deviation of the vapour from ideal gas behaviour is as follows:

$$(H^* - H) = \Delta H_s + \Delta H_g + \Delta H_{assoc} \tag{2}$$

where ΔH_s = enthalpy deviation for a " perfect fluid " comprised of spherically symmetrical molecules;

ΔH_g = the additional contribution due to the acentricity of the molecule;

ΔH_{assoc} = the enthalpy deviation due to association, in the case of polar molecules.

VOL. 2 1961

The first two terms in equation (2) can be determined by using the generalized correlation of Curl and Pitzer[3], since they contain only quantities pertaining to molecular geometry. For non-polar substances such as benzene and n-pentane only these terms need be used. When applied to polar substances the third term is also significant. For such substances the first two terms are determined by using the temperature and pressure of the associating substance and the critical constants and vapour pressure of the hydrocarbon homomorph.

The third term in equation (2) is treated by supposing that association accounts for all orientational effects in the substance not accounted for by molecular geometry. A number of assumptions are made in the evaluation of ΔH_{assoc}. Since this quantity is but a relatively small contribution to the value of $(H^* - H)$ in equation (2), these assumptions are not as serious as might be expected. The association is represented by the reaction

$$n\text{A} \rightleftharpoons \text{A}_n \tag{3}$$

Assuming the mole fraction of the polymers to be much less than one, the association effect is obtained from the individual heats of formation of the polymers, $\Delta H_{f,n}$, by the sum

$$\Delta H_{\text{assoc}} = \sum_{n=2}^{\infty} (-x_n \, \Delta H_{f,n}) \tag{4}$$

Utilizing the concept of the equilibrium constant and the van't Hoff equation, the final expression for ΔH_{assoc} is:

$$\Delta H_{\text{assoc}} = \sum_{n=2}^{\infty} - x_1^n P^{n-1} \, \Delta H_{f,n} \exp \frac{\Delta S_{f,n}}{R} - \frac{\Delta H_{f,n}}{RT} \tag{5}$$

If association between pairs of alcohol molecules to form dimers can be represented by the same kind of hydrogen-bonding process, the heat of formation of the dimer should be nearly the same for each of the alcohols. This is shown in *Table 1* where the heats of dimerization for methanol and ethanol from various sources are listed.

Table 1. Heats and entropies of formation for alcohol dimerization (from the literature)

Alcohol investigated	ΔH_{f_2} (B.t.u./lb.-mole)	ΔS_{f_2} (e.u.)
Methanol vapour[a]	− 5800	− 16·5
Ethanol vapour[b]	− 6120	− 16·57
Methanol vapour[c]	− 5400	—
Several different alcohols[d]	− 7200	—
Liquid mixtures of ethanol and methanol in carbon tetrachloride at 45°C:[e]		
Methanol	− 6340	—
Ethanol	− 4950	—
Ethanol[f]	− 5000	− 16·04

a Weltner and Pitzer[12]: low pressure P–V–T data, vapour heat capacity data and spectroscopic measurements.
b Barrows[4]: low pressure P–V–T data, vapour heat capacity data and spectroscopic data.
c Inskeep and Kelliher[5]: spectroscopic data.
d Kretschmer and Wiebe[1]: analysis of available P–V–T data for several alcohols.
e Barker, Brown, and Smith[1]: liquid solutions of methanol and ethanol in carbon tetrachloride at 45°C.
f Data for ΔH_{assoc} obtained from experimental data of this work.

This suggests a general procedure for calculating ΔH_{assoc} for various alcohols. The heat of dimerization would be chosen as −5,000 B.t.u./lb.-mole, as obtained for ethanol, and the entropy of dimerization evaluated to agree with the particular alcohol. No reliable method is available to estimate ΔS_{f_2}, but average values for methanol and n-propanol can be obtained from the enthalpy data and equations (2) and (5). The results, given in *Table 2*, indicate the magnitude for the entropy terms.

Table 2. The average entropies of formation for the dimers and trimers of methanol and *n*-propanol*

Alcohol	ΔS_{f_2} (e.u.)	ΔS_{f_3} (e.u.)
Ethanol	− 16·04	− 42·99
Methanol	− 16·11	− 44·55
n-Propanol	− 17·13	− 45·48

* Average values of entropy obtained from equations (2) and (5), using the heats of formation of the dimer and trimer for ethanol, $\Delta H_{f_2} = 5000$ B.t.u./lb-mole and $\Delta H_{f_3} = -20{,}800$ B.t.u./lb-mole.

This same procedure can be used to obtain the constants for the trimer and higher terms, taking $\Delta H_{f_3} = -20{,}800$ B.t.u./lb-mole as obtained for ethanol. The average values of ΔS_{f_3} for methanol and n-propanol so determined are also listed in *Table 2*.

The parameters listed in *Table 2* were used in equations (2) and (5) to calculate the enthalpy deviation from ideality for each alcohol. The results, when compared with the experimental data, indicate an average absolute error of less than 1 B.t.u./lb. for ethanol and n-propanol and 2·7 B.t.u./lb. for methanol. In comparison, conventional, generalized correlations[4, 7] applied to the data give average absolute errors of 5–15 B.t.u./lb.

PREDICTION OF ENTHALPY OF MIXTURES

The correlation for the enthalpy deviations of pure associating substances presented in this paper was based on isolating the effect of association from molecular geometry. An extension of this procedure to mixtures is possible, provided an adequate method is available to evaluate the geometric effect of an associating substance and hydrocarbons. The total enthalpy deviation is obtained by adding the geometric contribution and the association effect.

The geometric contribution to the mixture can be determined by combining the pure-component enthalpy deviations for the hydrocarbon and the hydrocarbon homomorph of the associating substance. The P–V–T properties of hydrocarbons are represented reliably to moderate pressures by the virial equation of state retaining only the second coefficient. Mayer[8] has shown that the second virial coefficient for a binary mixture is related to the pure component coefficients by the expression:

$$B_m = x_1^2 B_1 + 2x_1 x_2 B_{12} + x_2^2 B_2 \qquad (6)$$

VOL 2 1961

When the enthalpy deviation with pressure is calculated for the mixture, a similar expression is obtained for the relationship between the mixture and pure component enthalpy deviations.

$$\Delta H_m = x_1^2 \Delta H_1 + 2x_1 x_2 \Delta H_{12} + x_2^2 \Delta H_2 \qquad (7)$$

Equation (7) can be evaluated for the mixture by calculating ΔH_1 for the hydrocarbon homomorph of the associating substance and ΔH_2 for the hydrocarbon in the mixture. The generalized correlation of Curl and Pitzer[3] was used for this calculation. The geometric mean $\sqrt{\Delta H_1 \Delta H_2}$ was employed to evaluate the interaction parameter, ΔH_{12}.

Adding the association effect, ΔH_{assoc}, to the geometric contribution gives the following expression for the total deviation from ideality:

$$\Delta H_{ma} = x_1^2 \Delta H_1 + 2x_1 x_2 \Delta H_{12} + x_2^2 \Delta H_2 + \Delta H_{assoc} \qquad (8)$$

In applying this equation, ΔH_{assoc} may be obtained from equation (5), and the quantity x_1 may be taken as the mole fraction of the alcohol in the mixture. As in the case of correlating the pure component data, this is equivalent to assuming that the extent of polymerization is relatively small. Equation (8) was used to calculate the enthalpy deviations for the benzene–ethanol, n-pentane–ethanol and benzene–methanol mixtures.

Comparison with the measured results indicates an average absolute error less than 3 B.t.u./lb. for all mixtures. Also, the results are generally consistent and more accurate than those obtained from the generalized correlations using pseudo or true critical constants. The advantage of equation (8) as a predicting procedure is that it does not require mixture properties. The necessary interaction parameter, ΔH_{12}, is calculated from the pure component data.

Notation

B	Second virial coefficient
H	Enthalpy at any pressure; smoothed enthalpy data
L	Latent heat of vaporization
P	Total pressure
R	Universal gas constant
S	Entropy
T	Absolute temperature
W	Weight
x	Mole fraction
z	Compressibility factor, $z = RT/PV$

Superscripts

*	Ideal gas state

Subscripts

c	Critical property; calorimeter in equation (1)
f	Formation; " Freon 11 "
g	Geometric contribution in addition to spherical contributions
m	Mixture property; mixture
ma	Mixture containing an associating substance
n	Number of monomer units in a polymer

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TRANSFORMATIONS IN THE Ta–H AND Ta–D SYSTEMS

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INTRODUCTION

Elemental tantalum is known to dissolve large quantities of hydrogen or deuterium. In 1940 Kelley[1] published heat capacity data for tantalum and for tantalum containing 3, 6 and 9 atomic per cent of hydrogen. Excess heat capacities in the temperature range 100° to 300°K were observed for the binary system but not for the element. Diffraction studies by Waite, Wallace and Craig[2] were carried out in an attempt to ascertain the origin of Kelley's thermal anomalies. This study showed that at the concentrations employed by Kelley the system consists of two phases: the primary solid solution of hydrogen in tantalum (α-phase) and a second phase (β-phase) approximating the composition Ta_2H. Structure determinations showed the α-phase to be body-centred cubic. The β-phase was found to be similar. It is, however, slightly distorted in the c-direction so that its axial ratio is 1·008 and its structure is hence body-centred tetragonal.

It now seems clear that the anomalies observed by Kelley resulted from the conversion of the two-phase system at low temperatures into a single phase (α) at high temperatures. This process is endothermal and gives rise to the observed excess heat capacity.

These results answer the question as to the origin of Kelley's anomalies but pose another, perhaps more interesting, question. What is the essential difference between the α and β forms of Ta_2H? The α–β transformation, occurring at about 61°C, has been under intensive investigation in our Laboratory for a number of months. It has been studied by the following techniques: X-ray diffraction, neutron diffraction, electrical resistance measurements, magnetic susceptibility determinations, and measurement of internal friction. In addition, very recently heat capacity measurements have been made in the vicinity of the transformation temperature.

PHENOMENA WHICH COULD GIVE RISE TO THE α–β TRANSFORMATION

Two possibilities have received consideration. One, the 61°C transformation could be a Néel point. If so the conversion of the antiferromagnetic β-Ta_2H into paramagnetic α-Ta_2H, could be detected, at least in principle, by magnetic susceptibility determinations. Measurement of the susceptibility of Ta_2H by Cherry and Wallace[3] showed a temperature-independent

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susceptibility in the range of the α–β transformation and hence virtually excluded the possibility that the transformation is magnetic in origin.

The second possibility is that the transformation is due to the rearrangement of the hydrogens in the many-fold more abundant interstitial sites. That this is the case has been confirmed by neutron diffraction examination of Ta_2D. Patterns for Ta_2D were obtained* at 53°C and at room temperature, 78°K and 4·2°K. The pattern at 53°C shows a unit cell identical with that indicated by X-ray diffraction measurements. It contains 2 atoms of Ta and 1 atom of D. The patterns at the other temperatures indicated a unit cell with doubled parameters so that the cell has 8 times the volume of the X-ray unit cell and hence contains 16 Ta and 8 D atoms.

The enlargement of the unit cell immediately implies an ordering of the deuterium atoms at room temperature and below and suggests that the transition is an order–disorder transformation involving the interstitial hydrogens. This is also supported by measurement of the electrical resistance of a wire of Ta_2H. The resistance–temperature curve shows a sharp rise at the β–α transformation point.

ARRANGEMENT OF DEUTERIUM ATOMS IN THE Ta_2D SUPERLATTICE

It is, of course, of great interest to determine the arrangement of the deuterium atoms in β-Ta_2D. The first attempts to accomplish this by analysis of the neutron diffraction patterns were consistently unsuccessful. It began to appear that a fully ordered structure had not been achieved for any of the temperatures studied. It seemed as if some of the deuteriums were statistically distributed over more than one site even at liquid helium temperatures. This introduced a serious complication into an already complex problem.

To ascertain the number of alternative sites available, one could make use of residual entropy measurements which had been under way for Ta_2H in this Laboratory for a number of months. The residual entropy is evaluated by first obtaining the entropy change for the following reaction

$$2Ta_{(s)} + \tfrac{1}{2}\,H_{2(g)} \longrightarrow \alpha\text{-}Ta_2H_{(s)}$$

ΔS for this reaction may be evaluated by appropriate vapour pressure measurements in the range 300–400°C. Using the known entropies of the elements the entropy of α-Ta_2H at 300°C is computed. From this the entropy of β-Ta_2H at 0°K can be obtained if appropriate C_p data for Ta_2H are available. Details of the vapour pressure measurements and C_p determinations are given in later sections.

Preliminary estimates of the residual entropy indicated a value of R ln 2, suggesting that each hydrogen is statistically distributed over 2 sites. With this new information a satisfactory accounting for the neutron diffraction pattern was made with the deuterium atoms distributed over the tetrahedral interstices at 1/4 1/8 0, 1/8 3/4 0, 3/4 7/8 0, 7/8 1/4 0, 3/8 0 1/4, 5/8 0 1/4, 0 3/8 1/4, 0 5/8 1/4, 3/4 5/8 1/2, 5/8 1/4 1/2, 1/4 3/8 1/2, 3/8 3/4 1/2, 7/8 1/2 3/4, 1/8 1/2 3/4, 1/2 7/8 3/4, 1/2 1/8 3/4.

* Deep appreciation is expressed to Dr L. J. Corliss and his associates at the Brookhaven National Laboratory for providing these patterns.

VOL. 2 1961

HEAT CAPACITIES AND RESIDUAL ENTROPY OF Ta_2H

C_p values for Ta_2H have been determined in this Laboratory for the range 1·4° to 14°K (unpublished measurements of Galli, Sandmo and Craig[4]) and for 10° to 545°K (unpublished measurements of Saba, Sandmo,

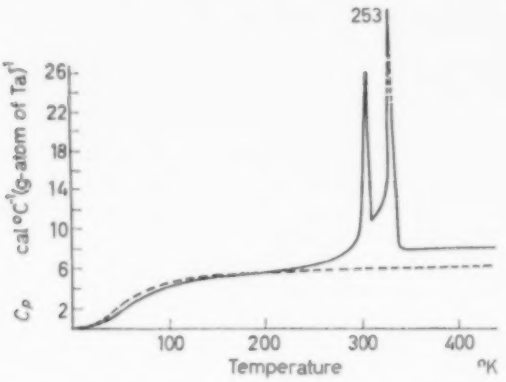

Figure 1. Temperature dependence of the heat capacity of Ta_2H: – – –, atomic heat capacity of Ta

Wallace and Craig[5]). These indicate the β–α transformation to be considerably more complex than had been originally assumed. The results (*Figures 1* and *2*) indicate that there are at least two and perhaps three forms of β-Ta_2H. The β_1 form exists below 37°C and β_2 from about 37° to 60°C. The double thermal anomaly at about 60°C suggests a third form, β_3.

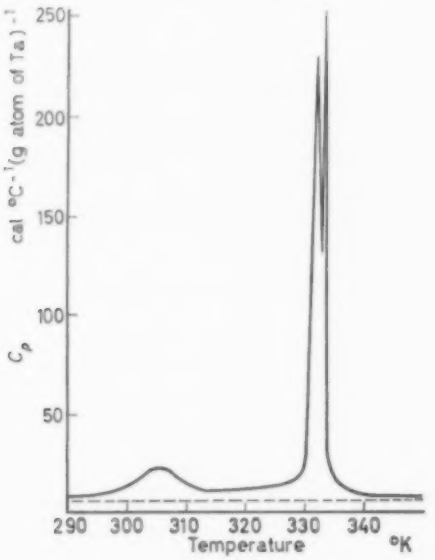

Figure 2. Heat capacities as functions of temperature: – – – Ta; — Ta_2H

The diffraction results indicate long-range order (with double site occupancy per atom) in β_1-Ta_2H. Long range order is destroyed at 37°C, giving rise to the thermal anomaly observed at that temperature. Extensive short-range order (undoubtedly pairing) is retained. In this instance the short-range order is seemingly highly co-operative and is largely destroyed in β-Ta_2H at 60°C, giving rise to the pronounced thermal anomalies at that temperature.

More recently final values of the residual entropy of Ta_2H have become available. In contrast with the result suggested by the preliminary estimate, the final values clearly indicate that $S_{0°K}$ for Ta_2H is $-0{\cdot}13$ e.u., with an estimated uncertainty of about 0·10 e.u. This indicates a unique arrangement of hydrogen atoms, a conclusion which contradicts that derived from the neutron diffraction pattern. This may signify that the arrangement of deuterium atoms cited in the earlier section is incorrect, but more likely implies short-range order (domain structure or the like) of the permitted occupancy in the β_1 structure. Support for this notion is provided by analysis of the 53° pattern. This pattern (for β_2-Ta_2D) is comparatively simple and can be interpreted with great confidence to indicate an arrangement which places 1/8 of a deuterium atom on the average in the tetrahedral interstices located at 1/2 1/4 0, 1/2 3/4 0, 1/4 1/2 0, 3/4 1/2 0, 0 1/4 1/2, 0 3/4 1/2, 1/4 0 1/2, 3/4 0 1/2. Superficially, this suggests a random distribution of the deuterium atoms over 8 sites. However, the observed configurational entropy of the β_2-Ta_2H is about 1/9 of the value expected if the deuterium atom were randomized over this number of sites. This indicates very extensive short-range order among the solute atoms.

VOL. 2 1961

VAPOUR PRESSURE MEASUREMENTS

The vapour pressure measurements show features which make them of interest quite apart from the issue of the residual entropy of Ta_2H. The results indicate that one is dealing with the single-phase primary solid solution up to the highest concentrations studied: $33\frac{1}{3}$ atomic per cent of hydrogen. Between 2 and 20 atomic per cent of hydrogen $\sqrt{P}$ is linear with N_H (P is the vapour pressure and N_H is the atomic fraction of hydrogen) in accordance with ideal solution behaviour for a dissociating solute. This behaviour, known as Sievert's law, is no longer observed either in concentrated solutions or in dilute solutions. The latter deviations are expected and rather surprising. Upon dilution below $N_H = 0{\cdot}02$ the observed vapour pressures first increase above, and then diminish so as to fall below, the values expected from Sievert's law. The data indicate a nearly constant partial heat of vaporization of about 9 kcal/g-atom of hydrogen for most of the composition range. Below $N_H = 0{\cdot}02$ this drops rapidly to a value of about 5 kcal/g-atom at the lowest measured concentration. Hence the partial molal enthalpy of hydrogen is anomalously high in dilute solutions. Analysis of the data shows that this is also true of its partial molal entropy. These departures from expected behaviour produce the observed deviations from Sievert's law. The source of the extra enthalpy and entropy is not yet clear. One likely possibility is that the behaviour of hydrogen in dilute solutions is fundamentally different from that in concentrated solutions. In the latter the hydrogen is known to be " solid-like ", that is it is localized

in an interstitial site for a time long compared with that required for one vibration. With dilution the site becomes smaller and, owing to Coulombic repulsion, the energy of the hydrogen becomes larger. Perhaps in sufficiently dilute solutions the energy of the hydrogen becomes sufficiently high for it to " sublime " out of the intersititial sites into the lattice, becoming " gas-like " in character. This would confer upon it extra entropy and extra enthalpy. Hence this type of transformation upon reducing the concentration could qualitatively account for the vapour pressure behaviour of the dilute alloys. Whether it actually occurs and is responsible for the observed deviations from Sievert's law must await the outcome of additional studies of this system.

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VOL.
2
1961

MAGNETIC TRANSITIONS AT LOW TEMPERATURES

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INTRODUCTION

In many crystalline substances there exists a pattern of electronic energy levels such that in the experimentally accessible range of temperature it is possible to pass from a low-temperature, completely ordered, form of essentially zero entropy to a higher temperature form where there is a nearly random distribution among several electronic states per molecular unit. There is, therefore, in the higher temperature form a substantial electronic contribution to the entropy of the crystal, of magnitude $R \ln n$ per mole, where n is the number of electronic states per molecular unit and R is the gas constant. Such a pattern of electronic energy levels is found in substances which the chemist would describe as having unpaired electrons and, in particular, in ionic crystals containing elements with partially filled d or f electronic shells. Because of the magnetic moment accompanying the spin and orbital angular momenta of the electrons, these substances are, in the higher temperature region, paramagnetic. The changes from the completely ordered low temperature form to a high temperature form where there is a random distribution among several electronic states may be called a magnetic transition. Such transitions always occur over an extended range of temperature and the increase in entropy of the electronic system (we shall for short call this the " magnetic entropy ") is never found to occur discontinuously at a single temperature as happens in the more familiar first order transitions associated with melting, vaporization or the change from one crystal form to another.

In this paper we shall choose for more detailed discussion some examples of magnetic transitions in salts of divalent ions of manganese, iron, cobalt and nickel. No attempt will be made at a comprehensive survey of the considerable amount of experimental and theoretical information concerning magnetic transitions in ionic crystals which has become available in recent years, nor will the more complicated phenomena of ferromagnetism and antiferromagnetism in metals be discussed. There are several excellent recent review articles on antiferromagnetism [1–4] and ferromagnetism[5]. The examples, chosen from among substances in which the writer and his collaborators have an experimental interest, will be typical of many magnetic salts at low temperatures. The main emphasis in this paper will be on the thermal properties rather than the many interesting phenomena disclosed by measurements of magnetic susceptibility, of magnetic structure by neutron diffraction, and electronic and nuclear resonance measurements.

SINGLE ION ELECTRONIC STATES IN A CRYSTAL

If an ion having a *d* electron is situated at a point of cubic symmetry in a crystal, then the five orbital states, degenerate in the free ion, are split into two levels, one group of three $d\epsilon$ orbitals having a symmetry corresponding to the irreducible representation t_{2g} of the group O_h, and the other group of two $d\gamma$ orbitals having the representation[6] e_g. If the positive ion is surrounded octahedrally by six negative ligands or by water molecules, as is usually approximately the case in ionic crystals of the iron group, then the $d\epsilon$ orbitals are lower in energy than the $d\gamma$ orbitals by the order of 10,000 cm^{-1}. With the exception of a few tightly bound complexes usually involving triply charged ions, the electrostatic repulsion energy among the electrons in ions containing several *d* electrons is more important than the octahedral field energy and the lowest state is the one of maximum spin quantum number, *S*, consistent with the Pauli principle. In *Table 1*

Table 1. Electronic levels of some transition metal ions in an octahedral field

Free ion configuration	*Octahedral field configuration*	*Spin*	*Orbital degeneracy*	*Divalent 3d ion*
d^5	$d\epsilon^3\ d\gamma^2$	5/2	1	Mn^{2+}
d^6	$d\epsilon^4\ d\gamma^2$	2	3	Fe^{2+}
d^7	$d\epsilon^5\ d\gamma^2$	3/2	3	Co^{2+}
d^8	$d\epsilon^6\ d\gamma^2$	1	1	Ni^{2+}
d^9	$d\epsilon^6\ d\gamma^3$	1/2	2	Cu^{2+}
d^{10}	$d\epsilon^6\ d\gamma^4$	1	1	Zn^{2+}

are listed the ground state configurations in an octahedral field, the maximum spin quantum number, *S*, and the maximum possible orbital degeneracy of the ground level consistent with these. Because of the large energy required to promote an electron from a $d\epsilon$ to a $d\gamma$ orbital the excited states involving such a promotion are never thermally occupied at temperatures reached in heat capacity measurements. There is further a spin degeneracy of $2S + 1$ and the total number of low-lying states is the product of the spin and orbital degeneracies. These states are split by crystal fields of lower symmetry and by the spin–orbit interaction energy[7, 8]. For the configurations d^5 and d^9 there is a single orbital state and consequently the maximum magnetic entropy that can be acquired at attainable temperatures is $R \ln (2S + 1)$. In the case of the remaining configurations (except the diamagnetic d^{10}) listed in *Table 1* it is possible to have orbital degeneracy in the ground state and the pattern of low-lying levels varies widely from one compound to another since it is critically dependent on the crystalline fields of symmetry lower than cubic.

When there is an even number of electrons in an ion it is possible for the crystalline fields of symmetry lower than cubic, combined with the spin–orbit interaction, to remove all degeneracy of the electronic states. An example of such a case is α-$NiSO_4 \cdot 6H_2O$ discussed below. When there is an odd number of electrons in an ion, however, a well-known theorem first formulated by Kramers[9] states that under the influence of crystalline fields and spin–orbit coupling each energy level is at least doubly degenerate. The residual magnetic entropy of $R \ln 2$ in the lowest

VOL. 2 1961

single-ion level, which by the third law of thermodynamics must vanish at the absolute zero, is lost through interactions between ions.

When the interionic interaction energies are weak compared with the splitting of the electronic levels by the crystal fields, then the magnetic entropy is lost gradually as the temperature is lowered. The magnetic heat capacity has the form of a Schottky curve, describable by a single-ion partition function. An example of such a case is that of α-$NiSO_4 \cdot 6H_2O$, whose heat capacity[10] in the range 1–12°K is shown in *Figure 1*. The observed heat capacity is the sum of a lattice heat capacity which will in this temperature region vary approximately as T^3 and a magnetic heat capacity derived from the partition function

$$Q = 1 + \exp(-\theta_1/T) + \exp(-\theta_2/T)$$

This partition function represents three states per Ni^{2+} ion, the two higher energy states having energies $k\theta_1$ and $k\theta_2$ above the ground state. The two parameters were chosen by a least-squares fit of the observed heat capacity data, after making a small correction for the lattice heat capacity, and the values $\theta_1 = 6{\cdot}44 \pm 0{\cdot}10$ deg and $\theta_2 = 7{\cdot}26 \pm 0{\cdot}10$ deg were obtained. The heat capacity curve calculated with these values of the parameters, shown as a solid line in *Figure 1*, agrees with an average deviation of 0·9 per cent with the twenty-four points between 1·1° and 5·8°K. The

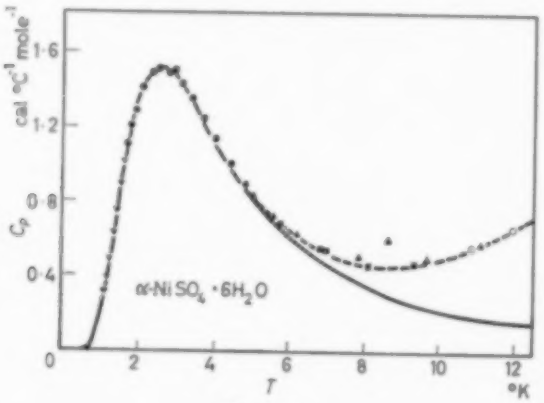

Figure 1

total magnetic entropy change agrees closely with the expected value of $R \ln 3$. Because of the very small lattice heat capacity of α-$NiSO_4 \cdot 6H_2O$ in the temperature range where the magnetic heat capacity is large, it is, in this substance, very easy to separate the magnetic and lattice contributions to the entropy. In many substances, however, there are similar gradual changes in magnetic entropy which occur at higher temperatures where the lattice heat capacity is large and there is appreciable magnetic heat capacity over a wide range of temperature. In such a case it is much more difficult to separate the magnetic and lattice contributions to the heat capacity and entropy.

INTERACTIONS BETWEEN MAGNETIC IONS

The interaction energy between different magnetic ions may be formally described as an exchange energy[3],

$$\sum -2\mathcal{J}_{ij}\vec{S}_i \cdot \vec{S}_j$$

where $\mathcal{J}_{ij}$ is the exchange integral between the ith and jth atoms and $\vec{S}_i$ and $\vec{S}_j$ are the respective spin angular momenta in units of $\hbar$. The exchange forces are short-range and act essentially only between near neighbours. In ionic crystals they are believed to be transmitted between positive magnetic ions *via* intervening closed-shell anions[11]. A positive $\mathcal{J}$ corresponds to a ferromagnetic interaction between two ions and a negative $\mathcal{J}$ to an antiferromagnetic interaction (lowest energy for the antiparallel spin alignment of the two atoms). The long-range dipole interactions between magnetic ions are anisotropic and often determine the direction of alignment of the magnetic moments relative to the crystal axes. The dipole energies in magnetically concentrated compounds are of the order of magnitude of kT at 1°K which may become energetically important in compounds such

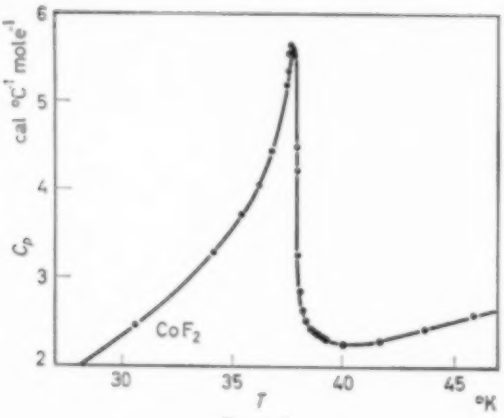

Figure 2

as $MnBr_2$ and $MnCl_2$ whose transitions occur in the helium temperature range. In many ionic crystals it is possible to divide the magnetic ions into two interpenetrating sub-lattices having opposite alignments of moments and arranged so that the neighbours of the ions of one sub-lattice belong to the other sub-lattice. Such an ordered arrangement was called antiferromagnetism by Néel[12] and an approximate statistical treatment equivalent to the Weiss molecular field approximation in ferromagnetism was given by Van Vleck[13]. According to this simple model the magnetic heat capacity and entropy in the antiferromagnetic state both increase with temperature until a critical temperature, called the Néel or Curie temperature, is reached. At this temperature the last trace of ordering among the magnetic ions disappears, the magnetic heat capacity drops abruptly to zero and the full magnetic entropy is acquired. Below the critical temperature the magnetic susceptibility of a single crystal measured

VOL. 2 1961

perpendicular to the direction of alignment of the antiferromagnetically ordered atomic moments is independent of temperature, while the susceptibility parallel to the direction of alignment drops with decreasing temperature below the critical temperature.

The observed effects in antiferromagnetic substances, the variations in magnetic susceptibility[3, 14], the long-range ordered structure as seen by neutron diffraction[15] and the observations of electronic[16] and nuclear[17] resonance in the ordered state are, for the anhydrous fluorides of manganese, iron, cobalt and nickel, in qualitative agreement with the simple model of Néel and Van Vleck. There is, however, quantitative disagreement, particularly in the neighbourhood of the critical temperature.

Typical heat capacity curves involving co-operative ordering of the magnetic moments are shown for CoF_2 (*Figure 2*)[18]; $MnBr_2$ (*Figure 3*)[19]; $CoCl_2$ (*Figure 5*)[20]; and $FeCl_2$ (*Figure 6*)[21]. Similar heat capacity anomalies involving co-operative ordering have been observed in MnF_2 [22], FeF_2 [18], NiF_2 [23], $MnCl_2$ [24], $NiCl_2$ [25] and many other compounds[3] containing magnetic ions. The general features of these heat capacity curves are a rise to a sharp peak considerably higher than would be found in a Schottky curve, and an abrupt drop at temperatures above the peak. There is always considerable magnetic heat capacity in the short-range order region above the maximum. Such an effect is expected from more elaborate statistical theories[26] of the antiferromagnetic transition but there is as yet no statistical theory which agrees quantitatively with experiment.

NATURE OF THE CO-OPERATIVE TRANSITION

Ehrenfest[27] classified transitions as first, second, third, *etc.*, order according to whether a discontinuity first appears in the first, second, third, *etc.*, derivatives, with respect to temperature and pressure of the Gibbs free energy. With the possible exception of $MnBr_2$ none of the co-operative transitions discussed above shows any evidence of a latent heat as would be found in a first order transition. Experimentally it is very difficult to prove whether there exists a discontinuity in the heat capacity (second order transition) or whether the heat capacity is continuous but has a discontinuous derivative. In order to investigate this point it is necessary to take heat capacity measurements involving a very small temperature rise and since there is always some finite instrumental limit to the precision with which temperature may be measured, a decrease in the temperature rise of a point results in a decreased accuracy and consequent greater scatter. With platinum thermometers in the range above 20°K the practical lower limit to the temperature rise in a measurement is about 0·05°K. If there is a discontinuity in heat capacity there will always be one point in a series which spans this discontinuity and which will fall between the upper and lower values of heat capacity at the discontinuity. In CoF_2 (*Figure 2*)[18] it was found that near the peak the heat capacity curve was definitely rounded at the top, involving a change in sign of the curvature of heat capacity *versus* temperature, and then appeared to drop very rapidly. In the other co-operative transitions listed above there is a similar rapid drop in heat capacity above the temperature of the maximum. It is not possible

to decide whether in this temperature region the heat capacity *versus* temperature curve has a mathematical discontinuity or merely has a rapidly varying but continuous shape. It is preferable to class the magnetic transitions along with the transition in liquid helium, that in ammonium chloride and order–disorder transitions in alloys as lambda-transitions[28] rather than try to decide the order in the Ehrenfest sense.

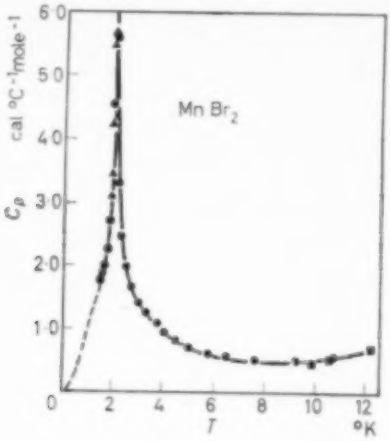

Figure 3

In $MnBr_2$ (*Figure 3*)[19] short points near the peak were measured which gave values as high as 30 cal $mole^{-1}$ $°C^{-1}$ for the heat capacity. In these points it was also observed that the approach to equilibrium was slow and the points did not fall on a smooth curve. In all the other magnetic transitions listed above there was no slowness in equilibrium near the peaks and no evidence of thermal hysteresis. It is probable that in $MnBr_2$ there is a latent heat or that the real heat capacity rises to extremely high values. The transition is not like the usual first order one, however, since the major part of the entropy change does not occur isothermally but is spread out over a large temperature interval.

ENTROPY CHANGES ASSOCIATED WITH THE CO-OPERATIVE TRANSITIONS

In the case of $MnCl_2$ [24] and $MnBr_2$ [19] the transitions occur in the liquid helium range and it is easy to make a sufficiently accurate correction for the small lattice contribution to the heat capacity. In both of these manganous salts the total magnetic entropy change is found to be R ln 6 in agreement with that expected for six closely spaced single-ion states coming from the spin of 5/2. In $MnBr_2$ half of this entropy change occurs in the region of short-range order at temperatures above the heat capacity maximum. $MnCl_2$ [24] is unusual in that there are two peaks in the heat capacity curve, and approximately one-third of the total magnetic entropy is acquired at temperatures above the upper peak. In the case of the other compounds the transitions occur at a sufficiently high temperature

so that the lattice contributions to the total entropy and heat capacity form an important fraction of the total and must be estimated with considerable accuracy in order to calculate the magnetic contributions to these thermodynamic quantities. Stout and Catalano[29] used data on the isomorphous diamagnetic compound ZnF_2, together with a corresponding states argument, to estimate the lattice contributions to the entropy and heat capacity of MnF_2, FeF_2, CoF_2 and NiF_2. The total magnetic entropy change in MnF_2, FeF_2 and NiF_2 is $R \ln (2S + 1)$. This indicates that in these salts there is a single low-lying orbital state and the splitting of the $2S + 1$ spin states by the crystalline field is small compared with kT at the transition temperature. In MnF_2, FeF_2, and NiF_2 between 70 and 90 per cent of the total magnetic entropy is acquired at the temperature of the heat capacity maximum. The variation with temperature of the magnetic entropy in these three fluorides is shown in *Figure 4*. In CoF_2, on the other

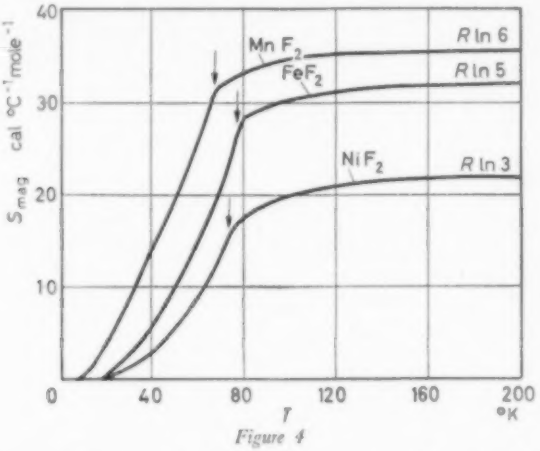

Figure 4

hand, the entropy acquired in the antiferromagnetic transition is $R \ln 2$, indicating that the ground state in the crystalline field is a Kramers doublet and that the energy difference to the next excited state is large compared with kT at the transition temperature of 37·70°K. This structure of electronic levels in MnF_2, FeF_2 and CoF_2 is consistent with the more detailed information given by paramagnetic resonance experiments[30] on dilute solutions of these salts in isomorphous ZnF_2.

In the compounds $FeCl_2$, $CoCl_2$ and $NiCl_2$ the magnetic ions are at positions of point symmetry D_{3d} and the threefold orbital degeneracy present in Fe^{2+} and Co^{2+} in a field of octahedral symmetry is partially removed, giving one doubly degenerate level and a singly degenerate one. Kanamori[31] has calculated the expected energy level pattern in $FeCl_2$ and concluded that if, as seems indicated by experiments, the doublet level lies lowest in energy, the total of ten low-lying electronic states will be split by the spin–orbit coupling into five pairs separated from one another by the magnitude of the spin–orbit coupling constant (100 cm^{-1} in the free ion). We have made use of heat capacity data on $MnCl_2$ [20] and $ZnCl_2$ [21] to estimate by the corresponding states method the entropy changes involved

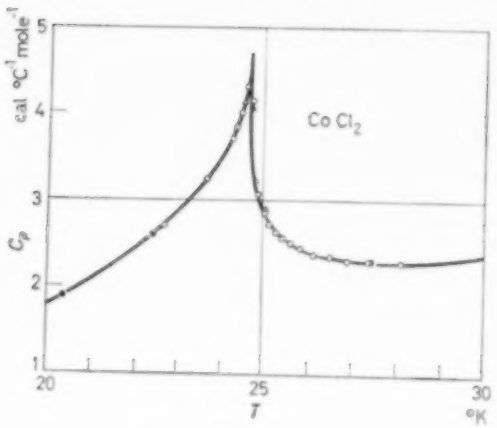

Figure 5

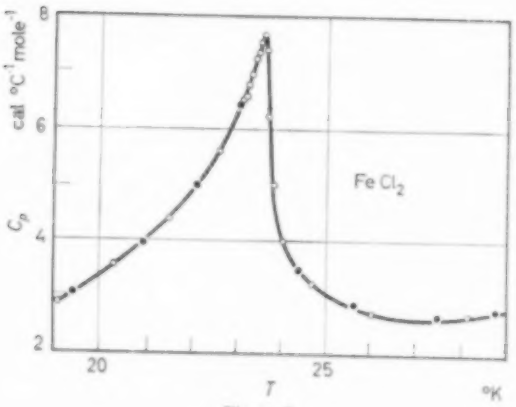

Figure 6

in the co-operative transitions. These are listed, together with the temperatures of transition and the corresponding data on the fluorides, in *Table 2*. The entropy change of R ln 2 in $FeCl_2$ is consistent with

Table 2. Data on magnetic transitions in some anhydrous fluorides and chlorides

Substance	*Temp. of* $C_{p\max}$ (°K)	*Entropy change of co-operative transition*	$2S+1$
MnF_2	66·5	R ln 6	6
FeF_2	78·35	R ln 5	5
CoF_2	37·70	R ln 2	4
NiF_2	73·22	R ln 3	3
$MnCl_2$	1·81, 1·96	R ln 6	6
$FeCl_2$	23·6	R ln 2	5
$CoCl_2$	24·7	R ln 2	4
$NiCl_2$	52·35	R ln 3	3

Kanamori's calculation[31] of the electronic energy level pattern. One would expect additional heat capacity, of the Schottky type, at temperatures above the observed anomaly (*Figure 6*) and extending up to several hundred degrees. At present it does not seem possible to estimate the lattice heat capacity of $FeCl_2$ at higher temperatures with sufficient accuracy to permit a reliable experimental estimate of this additional magnetic entropy which should amount in total to R ln 5. The entropy change of R ln 2 in $CoCl_2$ indicates that the lowest Kramers doublet is separated from the first excited level by an energy greater than kT at the transition temperature. Here also, one expects additional magnetic entropy gradually to be acquired at higher temperatures through the excitation of additional low-lying crystal field levels. In $NiCl_2$ [25] there is a single orbital level and the splitting between the three spin states is small compared with the interaction energy between ions, giving an entropy change of R ln 3 associated with the co-operative transition.

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VOL.
2
961

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DIE KRISTALLUMWANDLUNG DES KOBALTS

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Bei der α–β-Umwandlung des Kobalts, dem Übergang der hexagonalen in die kubisch dichteste Kugelpackung, handelt es sich um eine relativ selten auftretende Umwandlungsart, das sogenannte "Umklappen" ("turnover" transition), bei dem sich der Übergang in die andere Gitterstruktur nicht allmählich und längs einer Phasengrenze vollzieht, sondern im gesamten Kristall oder zumindest größeren Kristallbereichen spontan erfolgt. Ein solcher Vorgang ist naturgemäß nur dann möglich, wenn die Strukturänderung durch ein Gleiten von bestimmten Gitterebenen erreicht werden kann. Beim Kobalt ist diese Voraussetzung gegeben, und zwar ist durch eine Verschiebung der dichtest gepackten Ebenen gegeneinander der Übergang zwischen hexagonaler und kubischer Kugelpackung denkbar. Trotz zahlreicher veröffentlichter Arbeiten über das Verhalten des Kobalts erschien es angebracht—auch im Zusammenhang mit eigenen Arbeiten am Kaliumdichromat und an der Korksäure, die in dieser Hinsicht anloge Eigenschaften besitzen—, weitere Untersuchungen daran vorzunehmen.

Die zunächst auffallende Eigenart der Kobaltumwandlung ist ihre starke Verzögerung, die selbst bei Präparaten von außerordentlicher Reinheit beobachtet werden kann. Sie ist die Ursache dafür, daß die nach den üblichen Verfahren hergestellten Präparate im allgemeinen nicht aus einer reinen Modifikation bestehen oder sich doch zumindest nach einer einmaligen Umwandlung nicht wieder vollständig in die bei Zimmertemperatur stabile hexagonale Form zurückverwandeln. Diese Erscheinungen gaben sogar immer wieder dazu Anlaß, einmal die rein kubische, ein andermal die rein hexagonale Form in ihrer Existenz als thermodynamisch stabile Modifikation anzuzweifeln, da infolge des Zusammenfallens hexagonaler und kubischer Röntgenreflexe die gemessenen Intensitätsverhältnisse von den für die reinen Modifikationen berechneten abwichen.

Die Darstellung von reinem, pulverförmigem, hexagonalem Kobalt, das zuerst untersucht wurde, erfolgte durch Reduktion von Kobaltoxyd bzw. -formiat. Aus den erwähnten Gründen mußten dazu gewisse Bedingungen eingehalten werden. Es zeigte sich, daß man die reine α-Form erhält, wenn man die Hauptreduktion durch langsames Erwärmen auf höchstens 300° im Wasserstoffstrom durchführt. Zum Schluß kann dann zur ev. Vervollständigung der Reduktion noch bis 400° aufgeheizt werden.

Von solchen Präparaten wurden unter Wasserstoffatmosphäre zwischen Zimmertemperatur und *ca.* 800° bei schrittweisem Aufheizen (bzw. Abkühlen) Debye-Scherrer-Aufnahmen gemacht. Eine Umwandlung dieses sehr feinen Pulvers (Röntgenlinien diffus) war erst oberhalb etwa 600° feststellbar und erst knapp unterhalb 800° vollständig. Innerhalb dieses Bereiches nahm die Intensität der kubischen Reflexe (relativ zu den hexagonalen) entsprechend der schrittweisen Erhöhung der Temperatur von Aufnahme

zu Aufnahme ebenfalls schrittweise zu. Dabei spielte die Geschwindigkeit des Aufheizens keine Rolle. Wiederholte man nach einigen Stunden eine Aufnahme, die hexagonale und kubische Reflexe zeigte, bei derselben Temperatur, ohne zwischendurch die Temperatur verändert zu haben, so blieben die Intensitätsverhältnisse der kubischen zu den hexagonalen Reflexen unverändert. Beim Abkühlen—die Geschwindigkeit war hier ebenfalls ohne Einfluß—erfolgte keine feststellbare Rückbildung hexagonaler Form. Die Umwandlung eines pulverförmigen Präparates vollzieht sich also so, als ob die einzelnen Kriställchen eine verschieden große Hemmung zu Überwinden hätten. Da es sich um ein sehr reines Kobalt handelte, konnte diese Erscheinung nur dann auf Verunreinigungen zurückgeführt werden, wenn man annahm, daß schon geringste Mengen wirksam sind. Andererseits schien es möglich, daß die Kristallgröße bzw. Gitterstörungen einen Einfluß auf die Umwandlung haben könnten.

Um eine sichere Entscheidung fällen zu können, war es notwendig, kompakte Präparate von reinem α-Kobalt in einer für Debye–Scherrer-Aufnahmen geeigneten Form herzustellen. Dazu wurde dünner Platindraht mit einer genügend dicken Schicht von Kobalt auf elektrolytischem Wege überzogen, so daß unmittelbar aufnahmefähige zylindrische Präparate erhalten wurden. Zur Abscheidung der reinen hexagonalen Modifikation müssen auch hier bestimmte Bedingungen eingehalten werden. Insbesondere darf der pH-Wert eine untere, die Stromdichte eine obere Grenze nicht überschreiten. Die erhaltenen Präparate wiesen eine mehr oder weniger stark ausgeprägte Textur auf. Hauptsächlich wurden zwei Texturen erhalten. Bei der einen (I) lag die Fläche $(10\bar{1}0)$ parallel zur Zylinderachse des Präparats und damit senkrecht zur Feldlinienrichtung (Feldlinientextur), während außerdem die hexagonale Hauptachse eine stark bevorzugte Lage parallel zur Zylinderachse einnahm (wahrscheinlich infolge Strömung im Kathodenfilm). Bei der zweiten Textur war es gerade umgekehrt, hier lag die hexagonale Hauptachse senkrecht (Feldlinien senkrecht zu (0001)) und die $10\bar{1}0$ -*Richtung* parallel zur Zylinderachse. Die Textur II wurde nur bei Verwendung von reinster, gesättigter Kobaltsulfatlösung als Elektrolyt erhalten, während sich Präparate der Textur I in mehr oder weniger ausgeprägter Form aus den verschiedensten Elektrolyten niederschlugen.

Die Untersuchung solcher Proben, die aus Elektrolyten verschiedener Zusammensetzung und unter verschiedenen sonstigen erhalten worden sind, wurden auf die gleiche Weise wie die Pulverpräparate in einer Seemann-Hochtemperaturkammer unter reinem Wasserstoff während jeweils eines Umwandlungscyklus aufgenommen. Auch dabei erfolgte die Umwandlung beim Aufheizen und beim Abkühlen nicht sofort vollständig bei einer bestimmten Temperatur. Die vorhandene Menge neu gebildeter Modifikation nahm stetig mit steigender, bzw. fallender Temperatur zu. Dabei konnte die vollständige Umwandlung in die kubische Form, wenn bis 800° aufgeheizt wurde, immer erreicht werden, die vollständige Rückverwandlung erfolgte jedoch nur bei einigen Präparaten, die unter ganz bestimmten Bedingungen hergestellt worden waren. Eine sehr auffällige Erscheinung war die außerordentliche Kristallvergröberung, die sich häufig während der Umwandlung vollzog. Sie betrug immer mehrere Zehnerpotenzen,

VOL. 2 1961

so daß aus homogenen Debye–Scherrer-Linien, die häufig wegen der ursprünglichen Kleinheit der Kristalle sogar schwach diffus waren, nur noch eine mehr oder weniger große Anzahl voneinander getrennter Schwärzungspunkte auf dem Röntgenfilm erschienen. Diese Kristallvergröberung erfolgte ausschließlich bei Präparaten, die sich relativ leicht umwandelten, d.h. beim Aufheizen mindestens zwischen 500 und 550° in die reine kubische Form übergingen, bei diesen aber ausnahmslos. Dabei erfolgte die Vergröberung unmittelbar mit der Umwandlung. Hatte sich ein solches Präparat bei etwa 500° zum Teil umgewandelt, so waren die hexagonalen Reflexe nämlich noch homogen und, abgesehen von der geringeren Intensität, gegenüber den Aufnahmen bei niedrigerer Temperatur, überhaupt unverändert (z.B. Textur, Diffusität). Die daneben auftretenden kubischen Reflexe bestanden jedoch nur aus einzelnen Schwärzungsflecken. Die grobkristallinen Präparate zeigen nach der Rückverwandlung in die bei Zimmertemperatur beständige Form keine Textur mehr, ganz gleichgültig was für eine Orientierung vorher vorgelegen hat und wie stark sie ausgeprägt gewesen ist.

Wie erwähnt, wiesen die verschiedenen Elektrolytkobaltpräparate erhebliche Unterschiede in der Leichtigkeit (U.L.), mit der die Umwandlung erfolgte, auf, gemessen daran, bei welcher Temperatur die Umwandlung vollständig war und wie weitgehend sich die Rückverwandlung beim Abkühlen vollzog. Die Präparate mit der größten U.L. wurden aus Kobaltsulfatelektrolyten—besonders bei Gegenwart von Ammonium- oder Acetationen—erhalten. Verwendet wurden stets Elektrolyte mit hoher Co-Konzentration, i. a. gesättigte Lösungen, da ein möglichst gleichmäßiger und fest haftender Überzug notwendig war und Fremdinhibitoren tunlichst vermieden werden mußten. Die aus reiner Kobaltsulfatlösung, Ammoniumkobaltsulfat-Lösung und Kobaltsulfatlösung mit einem Zusatz von $\frac{1}{4}$ der Kobaltmenge an Kobaltacetat erhaltenen Präparate wandelten sich alle zwischen 500 und 550° vollständig um. Während jedoch die Präparate aus den letzten beiden Elektrolyten bei 500° schon zum großen Teil in der β-Form vorlagen, war bei denjenigen, die aus reiner Co-Sulfatlösung erhalten worden waren, noch keine Umwandlung eingetreten. Wurde vor dem Abkühlen nicht über 550° hinaus erhitzt, so war die Rückverwandlung jedes dieser Präparate (jetzt grobkristallin) zwar weitgehend, aber nicht vollständig; wurde jedoch kurz auf etwa 800° aufgeheizt, so hatten nach dem Abkühlen auf Zimmertemperatur nur noch die aus reiner Kobaltsulfatlösung erhaltenen Präparate Anteile von β-Modifikation. Durch mehrstündiges Tempern bei 800° oder kurzzeitiges Aufheizen auf etwa 1000° (immer unter Wasserstoff) konnte auch bei den letzteren praktisch vollständige Rückverwandlung erreicht werden. Diese Versuchsergebnisse schienen darauf hinzuweisen, daß der Grad der sekundären Inhibition bei der elektrolytischen Darstellung der Präparate eine gewisse Rolle spielt, der ursprüngliche Einschluß von Kobalthydroxyd also die U.L. herabsetzt. Daß eingeschlossenes Kobalthydroxyd diese Wirkung tatsächlich hat, wurde nachgewiesen. In einer Elektrolytlösung, die Präparate mit größter U.L. lieferte (Kobaltsulfat + -acetat) wurde mit einigen Tropfen Ammoniak etwas Hydroxyd gebildet und aus dieser Lösung ein Präparat hergestellt. Die Umwandlung desselben erfolgte erst bei 700° (gegenüber 500–550°), die

Rückumwandlung blieb völlig aus, und es trat keine Kristallvergröberung auf. Analog verhielt sich ein Präparat, das aus einer gesättigten Lösung von Kobalthydroxyd in Ammoniak erhalten wurde. Aus der letzten Lösung kann natürlich Kobalthydroxyd leicht adsorbiert werden.

Da Kobalthydroxyd—wenn nicht schon bei der Elektrolyse, so doch sicher unter den Bedingungen während der Hochtemperaturaufnahmen—reduziert wird, also als solches die Umwandlung kaum beeinflussen kann, muß wohl angenommen werden, daß bereits starke Gitterstörungen die Umwandlung erheblich hemmen können. Das steht auch in Einklang mit der starken Verzögerung der Umwandlung bei feinpulvrigen Präparaten. Alle bisher angeführten Elektrolytkobalte konnten durch Tempern bei 1000° unter Wasserstoff in Präparate mit großer U.L. übergeführt werden, wobei gleichzeitig auch die erwähnte Kristallvergröberung eintrat. Nur bei den Kobaltpulvern gelang das nicht.

Bei idealer dichtester Kugelpackung fallen bestimmte hexagonale Reflexe mit kubischen zusammen: (0002) u. (111), (11$\bar{2}$0) u. (220), (11$\bar{2}$2) u. (311), (0004) u. (222). Das ist bei den Reflexen niedriger Ordnung des Kobalts der Fall, bei denjenigen höherer Ordnung tritt aber eine Aufspaltung auf. So fallen die Reflexe (0004) und (222) nicht mehr zusammen, sondern tauchen bei Verwendung von Röntgenstrahlen mittlerer Wellenlänge (z.B. Fe_{K_α}-Strahlung) schon als zwei deutlich getrennte Reflexe in einigem Abstand voneinander auf. Dabei ist die Linie mit dem etwas größeren θ der hexagonale Reflex (0004). Der Abstand der dichtest gepackten Ebenen (ABAB . . ., ABCABC . . .) ist also in der hexagonalen Packung etwas kleiner als in der kubischen. Bei einer Anzahl von Präparaten, die bei Zimmertemperatur aus beiden Formen bestanden, fiel auf, daß häufig der Reflex (0004) nur sehr schwach auftrat oder völlig fehlte, obwohl aus anderen Reflexen zu erkennen war, daß sehr erhebliche Anteile hexagonaler Modifikation vorlagen. Nach den relativen Intensitäten sollte der Reflex (0004) jedenfalls stärker erscheinen. Da keine Anzeichen für eine bevorzugte Orientierung zu erkennen waren, die natürlich eine Veränderung der Intensitätsverhältnisse bewirken könnte, wurde vermutet, daß hier eventuell eine zweite hexagonale Struktur vorliegt, deren Reflex (0004) mit dem kubischen (222) zusammenfällt. Eine derartige Struktur entspräche exakt dem Modell einer idealen Kugelpackung. Man könnte sich vorstellen, daß sie durch Umklappen (Verschiebung der Ebenen ABC gegeneinander) unter Beibehaltung der Ebenenabstände der kubischen Struktur entstanden ist. Der Übergang in die gewöhnliche α-Form wäre nur eine Kontraktion der Gitterkonstanten c. Wenn eine solche Struktur neben kubischer und gewöhnlicher α-Form vorliegt, dann müßten auch die von einer Änderung der Gitterkonstanten c stark abhängigen Reflexe eine Aufspaltung aufweisen. Die Untersuchung mehrerer Präparate ergab, daß die in Frage kommenden Reflexe ((10$\bar{1}$2) und (10$\bar{1}$3)) zwar keine Aufspaltung mehr zeigen (der Effekt ist hier natürlich auch geringer als beim Reflex (0004)), aber eine sehr deutliche Verbreiterung gegenüber entsprechenden Präparaten der reinen α-Form. Sonst besteht kein Unterschied.

Um die Vorstellung der Umklappung durch Parallelverschiebung von Netzebenen (0001) bzw. (111) gegeneinander zu stützen, wurden schliesslich noch Versuche mit einem Kobalt-Einkristall gemacht, den wir der Freund-

VOL. 2 1961

lichkeit von Herrn Prof Krautz (Osram, Augsburg) verdanken. Er war als kubischer Einkristall aus der Schmelze gezogen worden und bestand bei Zimmertemperatur aus mehrerer (drei waren sichtbar) rein hexagonalen Bereichen. Aus einem von diesen wurde durch Aetzung ein stäbchenförmiges hexagonales Einkristallstück isoliert, mit dem dann experimentiert wurde. Es gelang, den Kristall mit der Normalen auf die Ebene (1010) senkrecht zur Drehachse zu justieren, sodass die Schichtebenen-Diagramme einfach wurden und bequem ausgewertet werden konnten. Nach Erhitzung auf 800°C (Umwandlung in einen kubischen Kristall) und Abkühlung (Rückumwandlung in die hexagonale Form) zeigten sich dann die Reflexe von 4 hexagonalen Kristallen oder Kristall-Bereichen. Aus den Schichtlinienwinkeln, unter denen diese auftraten, ergab sich, dass diese 4 Bereiche die 4 Raumdiagonalen [111] des aus dem ursprünglichen hexagonalen Kristall entstandenen kubischen Kristalls zu [0001]-Achsen haben, dass also tatsächlich (0001)-Schichten bei der Umwandlung kalt-heiss und in verschiedenen Bereichen alle 4 entstandenen (111)-Schichten bei der Umwandlung heiss-kalt aufeinander gleiten.

VOL.
2
1961

SOLID TRANSITIONS IN MIXED CRYSTALS OF ETHYLENE DICHLORIDE AND ETHYLENE DIBROMIDE

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INTRODUCTION

In principle, the heat capacity curve of a solid substance can give information about the dependence of energy absorption on temperature of the crystal lattice, and hence on the mechanism of any phase changes which occur therein. In practice, however, the amount of information is limited (a) by the fact that a considerable contribution to the measured C_p comes from the term β^2VT/α; (b) by the lack of an adequate theory of the heat capacities of complex crystals. In certain cases, though, considerable insight can be obtained by diluting the lattice of a compound which undergoes a phase transition with a second kind of molecule or ion, and observing the effect on the nature and magnitude of the transition. The added component has usually been one which itself has no transitions[1], but a few studies have been made of mixed crystals both of whose components exhibit solid transitions[2], when the phenomena are naturally more complex.

This paper concerns heat capacity measurements on mixtures of ethylene dichloride and dibromide, both of which undergo solid transitions, and form a continuous series of mixed crystals.

EXPERIMENTAL

The experimental method will be fully described elsewhere[3]. The calorimeter assembly was closely similar to that of Aston and Ziemer[4]. The calorimeter vessel, of about 70 cm^3 capacity, was freely suspended inside a copper " mantle ", itself suspended from a lead block inside an evacuated space. A re-entrant well in the calorimeter held a hollow former carrying a heating coil, inside which was a platinum resistance thermometer. The latter consisted of two strain-free spirals of 48 S.W.G. platinum wire, supported inside a platinum capsule. The thermometer was calibrated at the ice point and the boiling points of naphthalene, water and liquid oxygen. A double potentiometer of the type described by White was used for all the electrical measurements. The standard procedure for the measurement of heat capacities was followed. Determination of known thermal quantities showed that the absolute accuracy of the results was at least $\pm 0{\cdot}5$ per cent; the internal consistency was considerably better—about $\pm 0{\cdot}1$ per cent.

Ethylene dibromide and dichloride were carefully purified, finally by distillation from a 120 cm column packed with Fenske helices. The refractive index of the final sample of the dibromide agreed exactly with the value

quoted by Timmermanns[5], while the melting range of the dichloride showed it to contain only 0·03 mole per cent of liquid-soluble, solid-insoluble impurity. The samples were kept out of contact with moisture, and the filling of the calorimeter vessel was carried out in a dry-box.

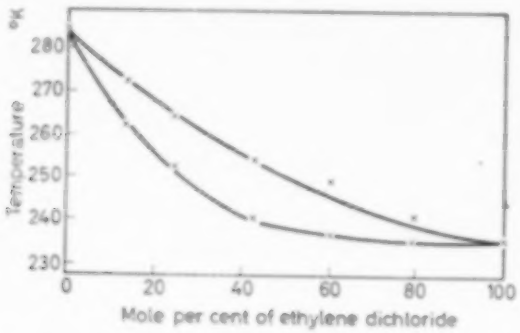

Figure 1. Freezing and melting curves for ethylene dichloride–ethlylene dibromide mixtures

The phase diagram for the ethylene dichloride–ethylene dibromide system[6] (*Figure 1*) shows that these compounds give a complete series of mixed crystals just below the melting curve. The liquid mixtures were frozen as rapidly as possible, in order to minimize phase separation on cooling, although to some extent this was obviously inevitable, and normally a mixture was not allowed to melt again until all measurements on it had been made. But in a few cases measurements were made on the same mixture before melting, and after melting and re-freezing, and the results were found to agree, provided the mixture had been annealed after each freezing, by the following method. The frozen mixture was cooled as rapidly as possible to well below the temperature of the lowest transition for the system, and was then heated to within a few degrees of its melting temperature, held there for some hours, and then cooled very slowly to below the temperature of the lowest transition. When a mixture had been taken three times through this heating and cooling cycle, it was possible to obtain a completely reproducible specific heat curve for the whole temperature range. For any mixture, as much as possible of the transition region was always covered by continuous working.

RESULTS

For any mixture at any temperature, the heat capacity quoted is the total heat capacity of the contents of the calorimeter, divided by the total number of gram-molecules present—that is, it is a mean molar heat capacity.

Figures 2 and *11* give the heat capacity curves for pure ethylene dibromide and dichloride[7], while *Figures 3–10* show the curves for the eight mixtures investigated. These contained respectively 3, 8, 18, 43·5, 51, 60, 80 and 90 mole per cent of ethylene dichloride. For the discussion of the results, four regions of interest may be distinguished.

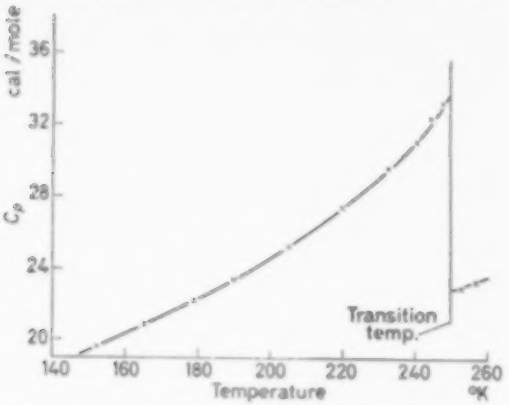

Figure 2. Heat capacity curve for ethylene dibromide

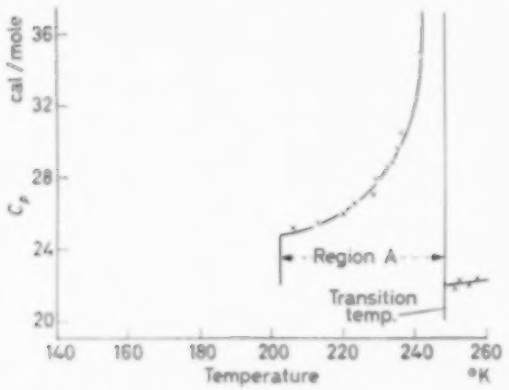

Figure 3. 3 mole per cent of ethylene dichloride

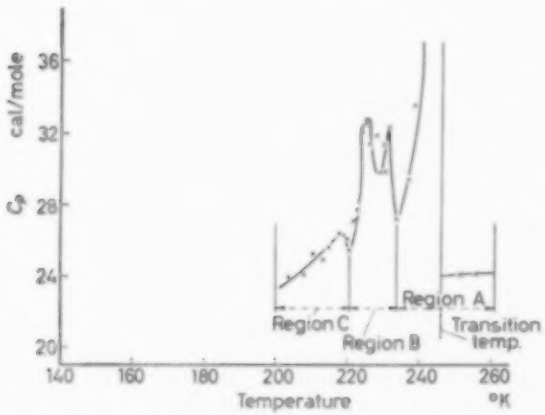

Figure 4. 8 mole per cent of ethylene dichloride

A. Around 250°K—Ethylene dibromide undergoes a sharp transition at 250°K which also appears (though at slightly lower temperatures) for the mixtures containing 8 and 18 mole per cent of dichloride.

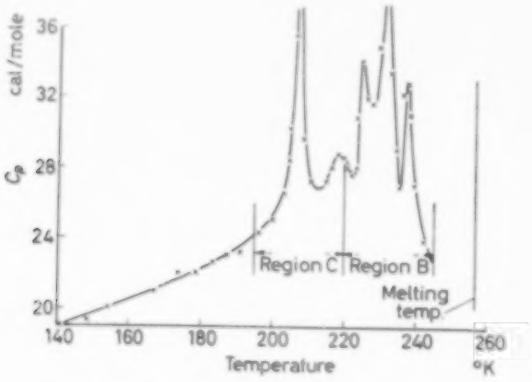

Figure 5. 18 mole per cent of ethylene dichloride

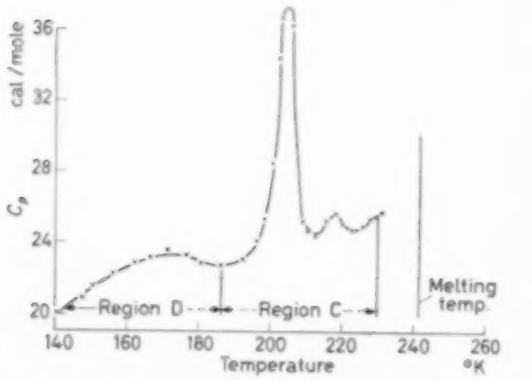

Figure 6. 43·5 mole per cent of ethylene dichloride

B. The range 225–235°K—For mixtures with 8 and 18 mole per cent of dichloride, this is a region of complexity, with two or three maxima in this part of the heat capacity curve.

C. The range 205–215°K—Mixtures containing from 18 to 60 mole per cent of ethylene dichloride have a marked, narrow maximum heat capacity at about 206°K, with a much smaller subsidiary peak about 10° higher.

D. Below 178°K—Ethylene dichloride has a very broad hump in its heat capacity curve, with a maximum at about 178°K. On addition of dibromide the height of this hump is reduced, while its breadth is more or less unaffected. For 90 and 80 mole per cent of dichloride the hump is as sharp as for the pure dichloride, while for the mixtures with from 43·5

VOL. 2 1961

to 60 mole per cent of dichloride the hump is appreciably more rounded. The temperature of the maximum is first depressed by addition of dibromide, but with increasing amounts again rises slightly.

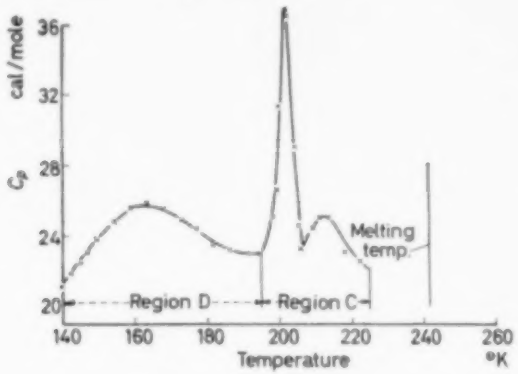

Figure 7. 51·0 mole per cent of ethylene dichloride

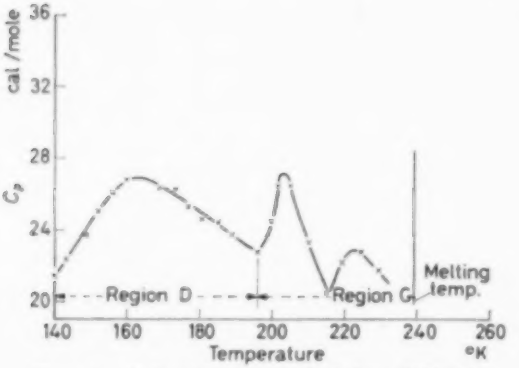

Figure 8. 60·0 mole per cent of ethylene dichloride

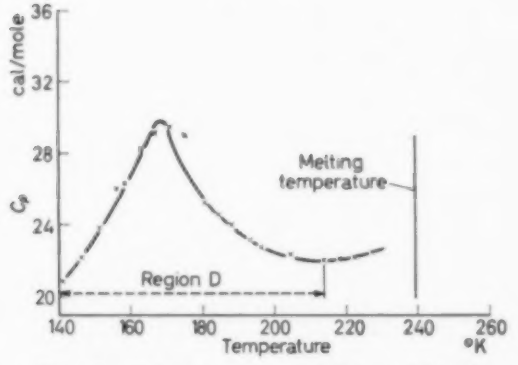

Figure 9. 80·0 mole per cent of ethylene dichloride

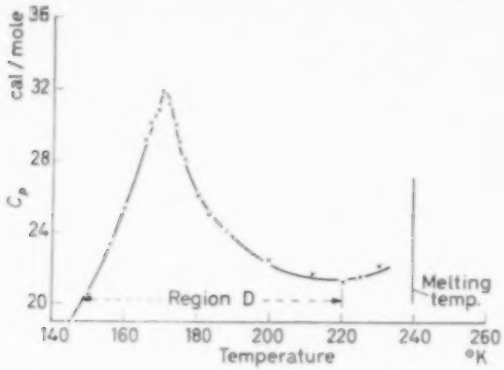

Figure 10. 90·0 mole per cent of ethylene dichloride

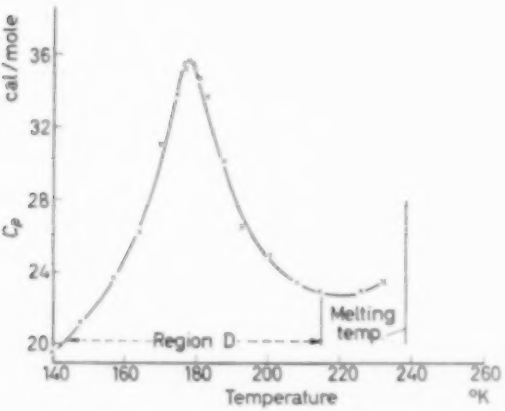

Figure 11. Heat capacity curve for ethylene dichloride

DISCUSSION

In the interpretation of these results, the following facts about ethylene dibromide and dichloride have to be borne in mind.

Ethylene dichloride crystallizes with a monoclinic space lattice containing two molecules per unit cell[8]. Infra-red absorption measurements[9] show the molecules to be in the fully-extended or "*trans*" configuration, while both X-ray and proton magnetic resonance measurements[8, 10] are consistent with the gradual transition at 178°K in the pure compound, marking the onset of free rotation of the ethylene dichloride molecules, probably about their axes of least inertia. Otherwise, the crystal structure is not affected by the transition. Ethylene dibromide has the same crystal structure as the dichloride (the β modification) above its sharp transition at 250°K, but exists in a different monoclinic form (the α modification) with four molecules to the unit cell, below this temperature[11]. As in the

case of the dichloride, the dibromide molecules are in the *trans* configuration and seem to be rotating as a whole above the transition point.

The sharp transition in pure ethylene dibromide is preceded by a seemingly anomalous rise in heat capacity, above the values to be expected from the curve at lower temperatures. Pitzer[7] suggested that this rise foreshadowed a second-order rotational change, similar to that in the dichloride. Because of greater lattice forces with the dibromide, molecular rotation was more difficult, the transition was accordingly delayed to a higher temperature, and before it could be completed, it gave place to a radical reorganization of the lattice, accompanied by a first-order anomaly. However, it is doubtful whether this view can be accepted, in the light of the information on the crystal structure of ethylene dibromide, which was not available to Pitzer. What can presumably be said, is that rotation is more difficult in the α-dibromide lattice than in the β-dichloride lattice.

Timmermanns' phase-rule study showed the formation of a continuous series of mixed crystals of ethylene dichloride and dibromide just below the freezing point, which is reasonable in view of the high temperature form of the dibromide having the same crystal structure as ethylene dichloride. Timmermanns did not report phase separation on continued cooling of the mixed crystals, but this is nevertheless likely to occur. When a crystal mainly of the dibromide is cooled, it will certainly undergo a lattice change at a temperature not much different from that for the pure dibromide. At lower temperatures, then, the dichloride molecules present will be in an " alien " lattice, and there will probably be a limit to the number which can be so accommodated, which may correspond to quite a small solubility of dichloride in dibromide. On the other hand, no such lattice change will occur when a crystal consisting mainly of dichloride is cooled. The dibromide molecules in such a crystal will therefore always be in a lattice which is at any rate the equilibrium lattice for dibromide at sufficiently high temperatures. Thus, though there must also be a solubility limit for dibromide in dichloride, it should be considerably greater than in the converse case. As will appear from consideration of the heat capacity curves, these solubility limits probably correspond to about 5 mole per cent of dichloride in dibromide, and 60 mole per cent of dibromide in dichloride. Hence, mixed crystals with less than about 5 or more than about 40 mole per cent of dichloride would remain homogeneous on cooling, while crystals of compositions between these values would separate into two components, of approximately these two compositions.

A further possibility is the formation of a super-lattice. If this should happen—most probably for mixed crystals with more or less equal proportions of each component—there would probably be a Curie point at some temperature, when the ordered, low-temperature arrangement, with the nearest neighbours of one kind of molecule predominantly those of the other kind, gave way to a disordered high-temperature form, in which the nearest neighbours were themselves a random mixture of the two components.

Because of these possible complications, it is only with mixed crystals containing relatively small proportions of either component that the effect of this component on the phase transition of the main component is likely

to be clearly discernible. Such replacement of the major component will (a) change the lattice spacing; (b) modify the lattice forces. The change in lattice forces will be partly due to the attendant change in lattice spacing, and partly due to the less symmetrical force field resulting from partial replacement. In addition, the actual intermolecular forces, for a given distance, will be changed. If these forces are mainly dispersion forces, they will be greater the larger the molecules concerned. If, on the other hand, the C–halogen bond dipoles make a sizeable contribution (although, of course, the molecules as a whole are non-polar in the *trans* configuration) then replacement of dichloride by dibromide may lead to a net reduction in intermolecular forces. The effect of replacement on forces and hence on transitions, cannot therefore be clear-cut. With these preliminary remarks in mind, the results for each of the four regions distinguished can now be considered.

Region A

If ethylene dichloride were soluble in the high-temperature (β) form of the dibromide (which has the same crystal structure) but insoluble in the low-temperature (α) form, small additions of dichloride should lower the dibromide transition point according to the equation:

$$\Delta T = \frac{RT^2}{\Delta H} \cdot \frac{n_2}{n_1}$$

Use of this equation, however, would indicate a lowering of about 8° for the addition of 3 mole per cent of dichloride, as against the observed lowering of less than 2°. Thus, it seems that the dichloride (as expected) must be to some extent soluble in the low-temperature form of the dibromide, so that the free energy of both α- and β-dibromide are lowered by addition of dichloride and the above equation does not apply. The less symmetrical force field in the mixed crystal should facilitate lattice transformation, which should therefore set in at a lower temperature than in the pure compound. For the same reason, the transition may not now be strictly isothermal, and experiment actually shows it to be less sharp than in the pure dibromide.

Region D

The unusual broadness of the rotational transition at 178°K in pure ethylene dichloride presumably means that the forces opposing rotation are small, so that the first molecules to rotate can do so quite easily, and no drastic loosening of the force field inhibiting rotation of the remaining molecules is thereby caused. The dependence on composition of the temperature of the "dichloride" transition is shown in *Figure 12*. For the replacement of up to 40 mole per cent of dichloride by dibromide, the transition temperature is lowered, which indicates that the lattice forces are decreased, presumably because the reduction in dipole–dipole attractions outweighs the larger dispersion forces to be expected, when dichloride is replaced by dibromide. The rise in transition temperature for more than 40 mole per cent of dibromide is understandable in terms of super-lattice formation, as is the change in the nature of the hump in

VOL 2 1961

the heat capacity curve between the 60 and 80 mole per cent mixtures, and these topics will be discussed in the next section.

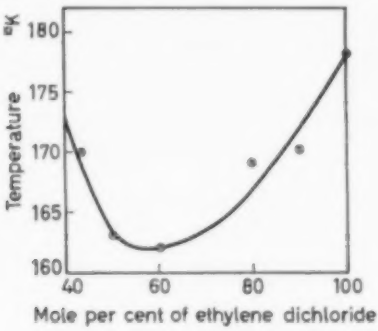

Figure 12. Variation of ethylene dichloride transition with composition

Region C

Phenomena in this temperature range differ from those discussed for the other temperature ranges, since the two interconnected peaks near 210°K occur for neither of the pure compounds. The lower peak, at about 206°K, might be due to onset of rotation of ethylene dibromide molecules, rotation having already set in for the dichloride in these mixtures. However, the shape of this peak is quite different from that occuring in the dichloride-rich mixtures, and its temperature varies very little with composition, unlike that of the dichloride peak. In addition, there is also the smaller subsidiary peak about 10° higher to be explained. For these reasons the 206° peak may more probably be associated with a super-lattice transformation. Although such a change will naturally be much more difficult for a molecular crystal than for an alloy, there seems no reason in principle why it should not also occur in this case—especially when the lattice forces have been loosened by a preliminary acquirement of rotational freedom. When there is a great disparity in the relative amounts of ethylene dichloride and dibromide, there will be little difference between an ordered and a disordered arrangement, and any super-lattice anomaly would be very slight. But with roughly equal proportions the anomaly should be more marked. It may therefore be significant that the 206° peak is found only for mixtures containing from about 40 to 60 mole per cent of dibromide, and also for the 82 per cent mixture, which is discussed in the next section. Further, the 206° peak is not dissimilar in shape to those usually found for super-lattice changes, and the small dependence of the transition temperature on composition is broadly consistent with the effect of composition on Curie point for certain alloy systems[12].

If mixed crystals with from 40 to 60 mole per cent of ethylene dichloride exist as super-lattices at low temperatures, each kind of molecule will then to a considerable extent be segregated on its own lattice and surrounded predominantly by molecules of the other kind. It may not be possible for ethylene dibromide molecules to rotate in such a situation, partly because

of their mutual isolation, making co-operative effects unlikely, and partly because dipole-dipole forces inhibiting rotation will be larger between an ethylene dibromide and an ethylene dichloride molecule than between two ethylene dibromide molecules. If de-segregation is responsible for the transition at 206°K the above factors then cease to operate, so that the smaller, higher peak may be caused by the onset of rotation for any non-rotating ethylene dibromide molecules. Its small magnitude may be due to full rotational freedom not even then being acquired, or to only a proportion of the dibromide molecules having had their rotation previously inhibited.

On this basis, mixtures with less than 40 mole per cent of dibromide will show no peak at 206°, for reasons already discussed. The dichloride peak is than as sharp as in the pure compound, and may indeed involve the rotation of dichloride and dibromide molecules alike, in the disordered crystal. From 40 to 60 mole per cent of dibromide, however, the mutual isolation of the dichloride molecules may well be responsible:

(a) For the change in character of the "dichloride" transition. It now becomes much smaller in area and more rounded in shape than for mixtures with less than 40 mole per cent of dibromide, possibly because the rotation now involves only the dichloride molecules.

(b) For the fact that the temperature of the transition now rises again, the coupling between dichloride molecules being lessened, by reason of their segregation.

Region B

The complex behaviour for mixtures with 8 and 18 mole per cent of ethylene dichloride in this region, is almost certainly due to the existence of a solid miscibility gap. As already discussed, the existence of such a gap, from about 5 to 40 mole per cent of dichloride, would result in a partial or complete separation in a cooled, annealed mixture with a gross composition falling between these limits, into an intimate aggregate of two mixed crystals, with respectively about 5 and about 40 mole per cent of dichloride. When such a mixture was heated, it would display the following features:

(a) A transition or transitions around 210°K, due to the 40 mole per cent component; this component might also show an ethylene dichloride transition at a lower temperature. In fact, the latter transition is only just apparent for the mixture with 43·5 mole per cent dichloride, so it may well be undetectable in the dichloride-rich crystal on that side of the miscibility gap, for a gross composition between the miscibility limits.

(b) One or more maxima, due to the absorption of energy on re-mixing to give a single mixed crystal.

(c) A dibromide-type transition, occurring at a temperature appropriate to the mixed crystal resulting from the re-mixing.

The critical (solid) solution temperature would probably lie not far below the melting curve for the system, so that process (a) should certainly occur before any re-mixing. Processes (b) and (c), however, might occur at about the same temperature, and the previous occurrence or non-

occurrence of re-mixing would obviously affect the temperature of process (c).

The above discussion has been in terms of complete separation and remixing, but fairly obviously this would not take place. It is considered that the annealing procedure used would produce at least a partial separation into two mixed crystals, possibly in domains of limited extent, and that there would be some degree of re-mixing across the domain boundaries on heating. In this case, the course of events would naturally be less clear-cut than that discussed above, and several maxima might appear as a result of the mixing process, instead of only one.

In fact, the mixture with 18 mole per cent dichloride does show peaks at 212° and 218°K, corresponding to those for the middle-range compositions. They are smaller than for the mixture with 44 mole per cent of dichloride, presumably because of the smaller amount of this component present, in the partially separated mixed crystal. Whether the isolated peak at 216°K for the 8 mole per cent mixture is also due to a 40 per cent component is perhaps more doubtful. On the other hand, the 8 mole per cent mixture has an unmistakable dibromide type transition at 247°K, which is not much lower than that observed for the 3 mole per cent mixture. This is quite understandable if the peak in the 8 mole per cent mixture is actually due to a 5 mole per cent component. That the 18 mole per cent mixture shows no dibromide-type peak is possibly due to the fact that the melting temperature for this composition is lower than the expected temperature of a dibromide transition, even for a 5 mole per cent crystal.

Confidence is therefore felt in attributing the broad features of the heat capacity curves for the 8 and 18 mole per cent mixtures to a partial separation into two mixed crystals, even though it is hardly possible to analyse these curves in detail.

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VOL.
2
1961

THERMODYNAMIC PROPERTIES OF INDANE AND INDENE

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INTRODUCTION

Over a score of years ago, Dolliver, Gresham, Kistiakowsky and Vaughan[1] measured the heat of catalysed hydrogenation at 100°C of indane and indene to the same hydrogenated product, which was presumed to be a mixture of isomers whose identity and concentration were not definitely established. The difference between these measured heat values is a measure of the heat of hydrogenation of indene to indane. More recently Naidus and Mueller[2] measured the equilibrium constants by a flow method for the system indane–indene–hydrogen from 375° to 535°C. From these equilibrium data these authors calculated the heat, entropy, and free energy changes for the hydrogenation reaction over the temperature range studied. Since the industrial importance of these materials has increased in the past few years, the following measurements were undertaken to extend our knowledge in this area. The heat capacities of indane and indene were measured from 15° to 320°K, and their heats of combustion were determined by standard bomb calorimetry.

EXPERIMENTAL

Materials

Indane—Commercial material was purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin, and was further purified by distillation. The equilibrium melting studies indicated the indane to be 99·89 mole per cent pure. The calorimetric sample weighed 62·245 g corrected to a vacuum basis and the molecular weight was taken as 118·179.

Indene—Commercial material was purchased from the Chemical Research and Intermediates Laboratories, Akron, Ohio, and was further purified by distillation. The equilibrium melting studies indicate purity in the range 99·7 to 99·9 mole per cent, although this has not been clearly established because of solid solution phenomena. The calorimetric sample weighed 63·900 g corrected to a vacuum basis and the molecular weight used was 116·163.

Calorimetric apparatus

Details of the automatic adiabatic calorimeter and its operation have been fully presented elsewhere[3, 4]. The sample container was of platinum,

joined with gold solder and contained a soft-glass cap which was sealed off to close the container hermetically. The container had a volume of about 70 cm^3 and contained a central platinum resistance thermometer with ten re-entrant heater wells about midway on equidistant radii. Twenty circular heat-distributing discs were bonded to the heaters but not to the resistance thermometer or side. For filling, the container was sealed to a glass vacuum line. After evacuation the sample was distilled in under its own vapour pressure, and the glass filling line sealed off after addition of a few cubic centimetres of helium gas. The quantity of glass used was weighed and corrected for.

The platinum resistance thermometer ($R_0 = 92\ \Omega$) was calibrated by comparison with another platinum resistance thermometer calibrated by the National Bureau of Standards, and thus reproduced the temperature scale described by Hoge and Brickwedde[5] and by Stimson[6]. The value 273·15°K was used for the ice point and 4·1840 abs. J has been used to define the calorie.

Heat capacity measurements

Comparison of heat capacity measurements on n-heptane[4] with the standard values reported by Ginnings and Furukawa[7] has shown that this automatic adiabatic calorimeter is accurate to within 0·25 per cent above 50°K, while below this temperature the uncertainty increases to as much as 1 per cent at 25°K. Additional comparisons of heat capacity values with other laboratories are in agreement with these findings.

Indane was cooled to about 12°K after which intermittent quantities of heat were added, finally raising the temperature to about 300°K. A sharp peak was observed in the heat capacity at about 70°K and fusion at about 222°K. After re-cooling to about 12°K, intermittent heating raised the temperature to about 70°K where the transition was again passed. After re-cooling some degrees below the transition, heat inputs were resumed with smaller increments through the transition range. After re-cooling a second time to below the 70°K transition, intermittent heat inputs were made until the temperature of the sample reached about 320°K. The fusion was carried out twice with continuous heating, after which the liquid range was measured to 310°K. Temperature rises were about 10 per cent of the absolute temperature below 50°K and 5° to 6° above, and were small enough so that curvature corrections were unnecessary.

Indene was cooled to about 12°K and was heated to about 290°K with intermittent heat inputs. After re-cooling to about 12°K intermittent heat inputs were made until 320°K was reached while the fusion was carried out with continuous heating. After re-solidification, the fusion was again accomplished with continuous heating. Indene has an abrupt rise in its heat capacity at about 125°K, similar to an annealing type of transition encountered with organic glasses, and in addition, a rather broad hump at about 210° to 250°K. *Table 1* lists thermal data derived from the smoothed heat capacity data on indane and indene read from smoothed curves drawn through the experimental points. Few of the experimental points were more than 0·2 per cent from the " best curve ".

VOL. 2 1961

Table 1. Derived thermal data

$T°$(K)	$C_p°$	$S°$ (cal mole^{-1}°K^{-1})	$\frac{H°-H_0°}{T}$	$-\frac{F°-H_0°}{T}$
		Indane		
15	1·86	0·72	0·53	0·19
20	3·24	1·45	1·03	0·41
25	4·68	2·32	1·62	0·71
30	6·03	3·30	2·24	1·06
40	8·30	5·35	3·48	1·87
50	10·28	7·42	4·64	2·78
60	12·26	9·47	5·75	3·72
80	14·43	14·04	8·15	5·89
100	16·10	17·43	9·57	7·86
120	17·84	20·52	10·80	9·72
140	19·68	23·40	11·97	11·42
160	21·66	26·16	13·06	13·10
180	23·79	28·84	14·13	14·70
200	26·04	31·46	15·21	16·25
220	28·43	34·05	16·30	17·75
240	40·70	46·71	26·76	19·95
260	42·14	50·03	27·89	22·14
280	43·80	53·21	28·96	24·24
298·15	45·47	56·01	29·92	26·09
300	45·65	56·29	30·01	26·28
320	47·79	59·31	31·06	28·25
		Indene		
15	2·13	0·91	0·66	0·26
20	3·42	1·71	1·19	0·51
25	4·66	2·60	1·76	0·84
30	5·77	3·55	2·34	1·21
40	7·64	5·48	3·44	2·04
50	9·09	7·35	4·43	2·92
60	10·35	9·12	5·32	3·80
80	12·48	12·40	6·72	5·67
100	14·22	15·38	8·05	7·32
120	16·02	18·12	9·22	8·89
140	19·35	20·86	10·45	10·41
160	21·54	23·56	11·70	11·85
180	23·64	26·22	12·91	13·30
200	25·81	28·82	14·09	14·09
220	28·56	31·40	15·28	16·12
240	31·42	34·01	16·50	17·51
260	34·02	36·62	17·74	18·88
280	43·25	48·43	27·92	20·51
298·15	44·68	51·19	28·89	22·30
300	44·84	51·47	28·99	22·48
320	46·54	54·21	30·06	24·14

RESULTS

Transition data

The heat capacity of indane begins to rise sharply at about 68°K and reaches a measured value of 138·88 cal mole^{-1} °K $^{-1}$ at 73·82°K: the value at 74·28°K has receded to 33·21 cal mole^{-1} °K^{-1}. By 78°K the heat capacity curve is rising smoothly again. Two separate runs through the transition region gave for the total heat absorbed between 68° and 78°K the values 187·0 and 186·1 cal/mole, indicating that the transition is reasonably reversible and free from hysteresis. Pre-melting seems to begin about 170°K and 180°K and becomes more pronounced as the melting point is approached. The heat of melting in the pre-melting region is about 0·3 to 0·5 per cent. The heats of melting for the four runs were 2054·8, 2056·0, 2054·8 and 2055·0, making the average value 2055 $\pm$ 2 cal/mole. Purity of the sample was calculated from melting data taken during intermittent melting, and tabulated in *Table 2* where F is the weight fraction melted. Our sample melted at 221·715°K, extrapolated to a pure melting point of 221·77°K, and gave a calculated purity of 99·89 mole per cent. The sample appears to behave ideally.

The shape of the solid heat capacity curve of indene does not give much of a clue regarding the presence or absence of pre-melting. The heats of melting for three runs were 2440·3, 2435·9, and 2437·7, making the average value 2438 $\pm$ 3 cal/mole. Purity calculated on the basis of the pre-melting heat capacity indicates about 99·95 mole per cent. Purity calculated from fractional melting data is tabulated in *Table 3* and indicates a purity of about 99·91 mole per cent although a plot of temperature *versus* the reciprocal of the fraction melted does not give a straight line, indicating that the

Table 2. Equilibrium fraction of indane melted (F) *vs.* temperature

T°(K)	F	$1/F$
221·438	0·129	7·74
221·570	0·238	4·20
221·616	0·351	2·85
221·651	0·463	2·16
221·673	0·575	1·74
221·687	0·690	1·45
221·703	0·800	1·25
221·714	0·909	1·10

Table 3. Equilibrium fraction of indene melted (F) *vs.* temperature

T°(K)	F	$1/F$
271·508	0·294	3·40
271·541	0·413	2·42
271·565	0·532	1·88
271·582	0·654	1·53
271·598	0·775	1·29
271·614	0·893	1·12

VOL. 2 1961

system departs rather widely from ideality. If the impurity forms a solid solution, application of the calculational method of Mastrangelo and Dornte[8] leads to a purity of 99·68 mole per cent. No one of these treatments is in agreement with all the facts, so the purity must be regarded as not established. The melting point of pure indene was taken as 271·70°K.

Entropy

Both heat capacity curves were extrapolated from about 15°K to 0°K by a combination of Einstein and Debye functions. For indane three degrees of Debye freedom with $\theta = 86°$ and three degrees of Einstein freedom with $\theta = 121°$ were used, while for indene three degrees of Debye freedom with $\theta = 77{\cdot}5°$ and three degrees of Einstein freedom with $\theta = 136°$. From 15°K to 198·15°K the heat capacity was graphically integrated. These entropy calculations are summarized in *Tables 4* and *5*.

Table 4. Calorimetric entropy of indane

	$S°$ (cal mole^{-1}°K^{-1})
0°K–15°K $\left[C_v = 3°\mathrm{D}\left(\frac{86}{T}\right) + 3°\mathrm{E}\left(\frac{121}{T}\right)\right]$	0·724
15°K–221·77°K (graphical)	33·555
Melting, 2055/221·77	9·266
221·77°K–298·15°K (graphical)	12·464
Entropy of liquid indane at 298·15°K	56·01 ± 0·10

Table 5. Calorimetric entropy of indene

	$S°$ (cal mole^{-1}°K^{-1})
0°K–15°K $\left[C_v = 3°\mathrm{D}\left(\frac{77{\cdot}5}{T}\right) + 3°\mathrm{E}\left(\frac{136}{T}\right)\right]$	0·912
15°K–271·70°K (graphical)	37·251
Melting, 2438/271·70	8·973
271·70°K–298·15°K (graphical)	4·053
Entropy of liquid indene at 298·15°K	51·19 ± 0·10

Vapour pressure

Vapour pressures were measured in a twin ebulliometer system in which the compounds and water boiled simultaneously at a common pressure. Equilibrium boiling temperatures were observed simultaneously for water and indane and for water and indene. The pressure in the system was calculated from the boiling temperature of the water, since the vapour pressure of water is well established. The experimental points were fitted by a least-squares method to the Antoine equation. The Antoine equation for indane: $\log P_{mm} = 7{\cdot}05483 - 1625{\cdot}70/(t + 211{\cdot}645)$, and for indene: $\log P_{mm} = 6{\cdot}87071 - 1507{\cdot}80/(t\ 195{\cdot}313)$, ($t$ + in °C), were used to calculate the vapour pressure values presented in *Table 6*.

Table 6. Vapour pressures of indane and indene

t(°C)	*Obs.*	*Calc.*	(*Calc.* − *Obs.*)
Indane pressures (mm)			
179·09	783·38	783·72	+ 0·34
178·04	763·03	763·75	+ 0·72
176·03	727·55	726·62	− 0·93
152·36	388·28	387·82	− 0·46
128·56	189·10	188·68	− 0·22
107·38	90·65	90·97	+ 0·32
91·68	49·60	49·56	− 0·12
Indene pressures (mm)			
183·82	783·11	782·90	− 0·21
182·72	763·03	762·32	− 0·71
180·79	727·81	727·23	− 0·58
156·95	387·81	389·36	+ 1·55
132·69	189·36	189·04	− 0·32
111·48	90·60	90·35	− 0·25
96·06	49·60	49·68	+ 0·08

Heats of combustion

Heats of combustion of the low-temperature samples were determined by standard bomb calorimetry[9]. The combustion calorimeter was calibrated with N.B.S. benzoic acid. Samples were enclosed in "Mylar" film to prevent evaporation and exposure to oxygen. All weights were corrected to true mass (weight in vacuum). Corrections to standard states of pure liquids and gases at one atmosphere were calculated by the method of Prosen[10]. Results are for 298·15°K and a constant pressure of one atmosphere. The heat of combustion refers to the reaction with oxygen to form liquid water ($\Delta H^{\circ}_{f,\,298^{\circ}K} = -68{\cdot}317$ kcal/mole), and gaseous carbon dioxide ($\Delta H^{\circ}_{f\,298^{\circ}K} = -94{\cdot}054$ kcal/mole). The heat of formation refers to the reaction of graphite and hydrogen to form liquid indane or indene. Atomic weights used were C = 12·011 and H = 1·0080. The values given in *Table 7* are the averages of five combustions on each material.

Uncertainties are equal to twice the overall standard deviation.

Table 7. Heat of combustion and formation of indane and indene at 298·15°K

	ΔH_c (kcal/mole)	ΔH_f (kcal/mole)
Indane (liquid)	− 1190·63 ± 0·47	+ 2·56 ± 0·47
Indene (liquid)	− 1146·15 ± 0·30	+ 26·39 ± 0·30

The difference between the values in the third column of *Table 7* represents the heat of hydrogenation of liquid indene to form liquid indane, which is − 23,830 ± 770 cal/mole. Dolliver, Gresham, Kistiakowsky, and

VOL. 2 1961

Vaughan[1] measured the heat of hydrogenation of indene to indane in the gas phase at 373°K, and reported $-24{,}200 \pm 500$ cal/mole. Since the heats of vaporization for indane and indene are expected to be similar, these heats of hydrogenation are in agreement within experimental error.

Thermodynamic properties at 298·15°K

The entropy and heat of formation data given above may be combined with the entropies of the elements[11] to calculate free energies of formation of indane and indene. Thermodynamic properties of *o*-ethyltoluene were taken from the compilation of the American Petroleum Institute Research Project 44[12]. These thermodynamic properties are summarized in *Table 8*.

Table 8. Thermodynamic properties at 298·15°K

	ΔF_f° (kcal/mole)	ΔH_f° (kcal/mole)	S° (cal mole^{-1}°K^{-1})
o-Ethyltoluene (liq.)	27·97	− 11·11	68·42
Indane (liq.)	36·06	2·56	56·01
Indene (liq.)	52·02	26·39	51·19
Hydrogen (gas)	0	0	31·21

On the basis of these data, the extent of two reactions at thermodynamic equilibrium has been calculated.

$$o\text{-Ethyltoluene} \rightleftharpoons \text{Indane} + \text{Hydrogen} \qquad \text{(i)}$$

Reaction (i) indicates the cracking of liquid *o*-ethyltoluene at 25°C to form liquid indane and hydrogen gas:

$$\Delta F_{R,\,25°C} = 36{\cdot}06 - 27{\cdot}97 = +\,8{\cdot}09 \text{ kcal}$$
$$\Delta H_{R,\,25°C} = 2{\cdot}56 - (-\,11{\cdot}11) = +\,13{\cdot}67 \text{ kcal}$$
$$\Delta S_{R,\,25°C} = 56{\cdot}01 + 31{\cdot}21 - 68{\cdot}42 = 18{\cdot}80 \text{ cal/°K}$$

The free energy change indicates that no indane would be formed at room temperature, but the large positive entropy change indicates that indane formation would be favoured at higher temperatures. Assuming that the heat and entropy changes in the reaction remain reasonably constant with temperature and that the heats of vaporization at 25°C are comparable, calculation shows that the free energy change for the reaction, ΔF_R, should be equal to zero at about 750°K (480°C). This means that roughly equal amounts of *o*-ethyltoluene and indane would be present at that temperature, and that above 750°K the formation of indane becomes increasingly favoured. Experience has shown that the assumptions regarding the constancy of ΔH and ΔS are reasonable.

For the reaction of dehydrogenating liquid indane to indene liquid and gaseous hydrogen:

$$\text{Indane} \rightleftharpoons \text{Indene} + \text{Hydrogen} \qquad \text{(ii)}$$

$$\Delta F_{R,\,25°C} = 52{\cdot}02 - 36{\cdot}06 = +\,15{\cdot}96 \text{ kcal}$$
$$\Delta H_{R,\,25°C} = 26{\cdot}39 - 2{\cdot}56 = +\,23{\cdot}83 \text{ kcal}$$
$$\Delta S_{R,\,25°C} = 51{\cdot}19 + 31{\cdot}21 - 56{\cdot}01 = +\,26{\cdot}39 \text{ cal/°K}$$

Here, also, the free energy change indicates that the dehydrogenation of indane to indene does not occur to any measurable extent at room temperature. Again, however, the large positive entropy change indicates that indene formation should be favoured at higher temperatures. Making the same assumptions regarding the constancy of ΔH and ΔS and again assuming the heats of vaporization to be comparable, the free energy change in reaction (ii) should be zero at about 900°K (630°C). In the temperature range 600°C to 750°C, these results indicate that roughly equal amounts of indane and indene may be present around 600°C, but at 750°C indene should be favoured over indane by a ratio of almost ten to one.

Naidus and Mueller[2] have presented an experimental study of the indene–indane–hydrogen system from 375°C to 525°C. Their results are in reasonably good agreement with these thermodynamic calculations, but indicate that ΔF for reaction (ii) should be equal to zero at about 530°C, about 100° lower than our calculated value. Considering the errors involved, we are inclined to average the two sets of results and conclude that indane and indene will be present in roughly equal amounts at about 580°C. Above this temperature, of course, indene predominates.

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VOL. 2 1961

ORTHO-PARA AND ISOTOPE SEPARATIONS BY PREFERENTIAL ADSORPTION AT LOW TEMPERATURES

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SUMMARY

Although the catalysed *conversion* of ortho- to para-hydrogen has been known for many years, the *separation* of the two species by adsorption at low temperatures is a much more recent discovery. The separation of the spin species was first clearly recognized by Sandler[1] during a study of hydrogen adsorption, at 90°K, on rutile and charcoal. The difference in extent of adsorption of ortho- and para-hydrogen was attributed to such strong hindrance of rotation of adsorbed hydrogen that one degree of rotational freedom is lost. A much more extreme example of the strong preferential adsorption of ortho-hydrogen at 20·4°K was encountered by Cunningham and Johnston[2] during the course of a study of the rate of conversion of ortho- to para-hydrogen by paramagnetic salts adsorbed on an inert support of finely divided alumina. The conversion rate was found to be nearly independent of the ortho–para composition of the liquid hydrogen mixture in contact with the catalyst. This suggested that the catalyst surface was almost completely covered with ortho-hydrogen. A detailed analysis led to an ortho–para separation factor of 16 ± 3 at 20·4°K. That ortho-hydrogen is preferentially adsorbed was established conclusively by Cunningham, Chapin and Johnston[3] as the result of experiments in which nearly pure ortho-hydrogen was prepared by successive adsorption and desorption on alumina in the absence of a paramagnetic salt. Para-deuterium was also separated by the same method. For both hydrogen and deuterium, molecules in the rotational state $J = 1$ are most strongly adsorbed. Separation of ortho- and para-hydrogen has also been observed by Moore and Ward[4] using the method of gas chromatography.

Recent adsorption experiments in this laboratory using γ-alumina free of paramagnetic materials have confirmed the magnitude of ortho–para separation factors suggested in the work of Johnston *et al.*[2, 3] These have been found to be dependent on surface coverage, so a single value cannot be given. However, they fall in the range 6–13 for hydrogen and 1·8–3·0 for deuterium. It has also been found that the hydrogen isotopes, deuterium-hydrogen, can be separated by preferential adsorption[5] with separation factors ranging from 5 to 200, depending on surface coverage. In addition, it has been observed that the magnitude of the isotope separation depends on the ortho–para concentration of each of the hydrogen isotopes undergoing separation.

The above experimental results have been accounted for by White and Lassettre[6] in a recent article in which a theory is developed by considering

the energy levels of a three-dimensional rotator. The Schroedinger equation for an adsorbed molecule on a plane surface has been solved for several simplified potential fields, leading to rotational and vibrational energies as functions of barrier height. The calculated separation factors, both ortho–para and isotope, are not in accurate quantitative agreement with the experimental results at a fixed surface coverage. However, the theory does predict all the effects observed to date, namely,

(1) molecules in the rotational state $J = 1$ (ortho-hydrogen, para-deuterium) are more strongly adsorbed than molecules in the ground state;

(2) predicted isotope separation factors are strongly dependent on the ortho–para composition of the isotope mixture.

Both the experimental and theoretical investigations are continuing in this laboratory in order to further elucidate the nature of the interactions of diatomic molecules, both heteronuclear and homonuclear, with surfaces[7].

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CONDENSED SOLUTIONS OF THE RARE GASES

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The condensed rare gases have a number of properties which make them suitable substances for an experimental test of solution theories. Their molecules have spherical symmetry and have no internal motions and their "radii" may differ by as little as 7 per cent. With the exception of helium, the rare gases crystallize in the same form—face-centred cubic.

Measurements of the total vapour pressure of solid solutions of the two systems A–Kr and Kr–Xe have been reported[1–4]. These measurements have been compared with theory and in particular with the average potential model theory developed by Prigogine and his associates. This theory leads to an expression for the excess molar free energy (G_E) of the form:

$$G_E = \sigma x_1 x_2 \qquad (1)$$

where x_1 and x_2 are mole fractions of the components and σ is a function of temperature (but not of composition) which may be calculated from a number of properties of one component. When σ is positive, as it is for the two systems considered here, there exists a critical temperature T_c, below which the components are insoluble for some values of the composition. The value of the critical temperature, T_c, is given by $T = (1/2R)\sigma$. From the measured vapour pressure, P, at several temperatures, T, σ may be determined as a function of T. The temperature T_c at which $\sigma = 2RT$ may thus be estimated. The values of T_c so calculated[1, 2] are shown in *Table 1*. No direct experimental evidence of the existence of two solid phases has been obtained for either the A–Kr or the Kr–Xe system. Some recent experiments with the latter system in which *indications* of a phase separation have been observed, are described below.

In the investigations of A–Kr solutions by Walling and Halsey[2] and Kr–Xe solutions by Freeman and Halsey[1] an amount of the heavier gas was condensed into a thermostated vessel at a temperature T_1. Subsequently, amounts of the other component were condensed into the same vessel. The solid mixtures were allowed twenty-four hours to attain equilibrium before the vapour pressure was measured. From these measurements a mean value of σ, $\bar{\sigma}$ for solutions of different compositions was calculated for each value of T_1. These values of $\bar{\sigma}$ are compared with the prediction of the average potential theory in *Table 1*. Considering the nature of the theory, the agreement is good.

In the author's experiments the two gases were mixed in the gaseous state and condensed into a calorimeter which was subsequently heated. Vapour pressure measurements were made at intervals during the heating

period (6–10 h). The measurements were extended through the heterogeneous region until the mixtures were liquid. By this means the solidus and liquidus curves were determined. In the case of A–Kr mixtures the measurements were found to be inconsistent with equation (1), *i.e.* σ as calculated by this equation was a function of composition. Nevertheless, the actual magnitude of the vapour pressure predicted by the average potential theory is in very good agreement with the observed vapour pressure[3, 4].

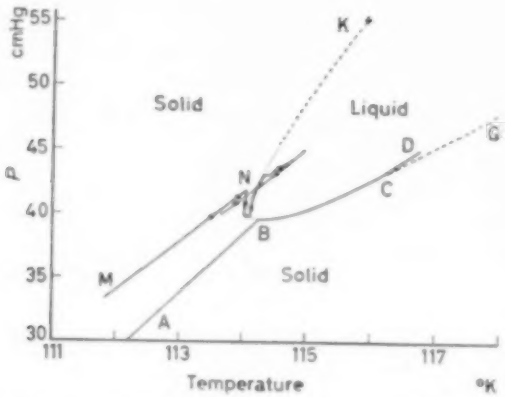

Figure 1. The P–T diagram for Kr–Xe mixtures: K, triple point of xenon, KBCG three-phase curve, ABCD and MN, curves for mixtures for which $x = 0{\cdot}28$ and $x = 0{\cdot}11$ respectively

The Kr–Xe system has been examined by the same method in the range $x = 0$ to $x = 0{\cdot}44$ where x is the mole fraction of xenon. In *Figure 1*, the P–T graph ABCD of a mixture of composition $x = 0{\cdot}28$ is shown (P = the total vapour pressure at the temperature T). The phases present in the mixture are: along AB solid and vapour, along BC solid, liquid and vapour and along CD liquid and vapour. The three-phase portions (BC, in this case), for *all* mixtures lie on the continuous curve KBCG. The liquid–solid phase transition points from which the phase equilibrium diagram, *Figure 2*, is drawn may be discovered from the intersection of the curves AB and DC with the three-phase curve.

Within the ranges $0 < x < 0{\cdot}04$ and $0{\cdot}27 < x < 0{\cdot}44$ the P–T graphs were of the form ABCD, *i.e.* the phase transition points and the three-phase curve were well defined. In the intermediate range $0{\cdot}04 < x < 0{\cdot}27$ irregularities in the P–T curves make the exact form of the solidus and liquidus and three-phase curve (shown dotted in this region in *Figure 1*) uncertain. It is quite possible that a eutectic point exists, in which case the three-phase curve would have a cusp at $P \simeq 40$ cm Hg and $T \simeq 114$°K.

The uncertainty in both *Figures 1* and *2* arises from irregularities in the results obtained for all mixtures in this range, as exemplified by the curve MN for a mixture $x = 0{\cdot}11$. As this mixture was heated a sudden fall in P, accompanied by an absorption of heat, was observed. After the mixture had melted completely the calorimeter was cooled and the subsequent behaviour of the mixture may be seen from *Figure 1*. (The behaviour of

these mixtures on cooling is not properly understood and is now the subject of further investigation.) Many mixtures within this intermediate range have been examined and all the P–T curves take the same form as MN on *Figure 1*. The maximum absorption of heat recorded is approximately 90 J/mole. It may be seen from *Figure 2* that the measurements of Freeman and Halsey do not cover this region of the phase equilibrium diagram.

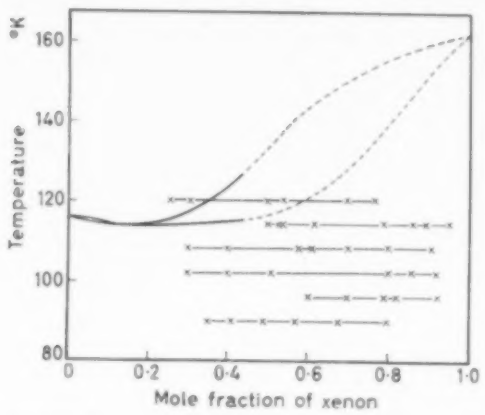

Figure 2. The solid–liquid phase equilibrium diagram of the Kr–Xe system. Measurements of vapour pressure were made at points marked by crosses by Freeman and Halsey[1]

The behaviour of the mixtures within this limited range of composition is consistent with the assumption that the gases, on condensation, form a two-phase solid mixture, the pressure fall and absorption of heat being associated with a transition to one single solid phase. To test whether an inhomogeneous mixture was created solely by the method of condensation used, the condensation temperature was varied between 65°K and 110°K. In all cases the measured P–T curves took the same form. Since, however, the solid mixtures are clearly not in a state of thermodynamic equilibrium, it is not possible to assert that the existence of a stable two-phase region in the phase equilibrium diagram of the Kr–Xe system has been demonstrated.

Table 1. Solid solution data compared with theory

System	$\bar{\sigma}$ (J/mole)		*Temp.* (°K)	*Ref.*	T_c *estim.* (°K)
	Exp.	*Calc.*			
Argon–krypton	750	685	83	2	56 ± 8
Krypton–xenon	1350	2320	105	1	91 ± 2

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VOL.
2
1961

LOWER CRITICAL SOLUTION POINTS IN HYDROCARBON MIXTURES

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It is common for the mutual solubility of a pair of liquids to increase with temperature until miscibility is complete at a critical solution point. Perhaps the best known systems of this kind are mixtures of hydrocarbons with polar liquids such as aniline and nitrobenzene, in which the upper critical solution temperature (U.C.S.T.) is often used as a check on the identity and purity of the hydrocarbons. The explanation of this phase behaviour is simple. The mean energy of interaction of a pair of molecules of one of the pure components is large because of their polarity. It is therefore energetically difficult to dilute such a liquid with a non-polar one. As the temperature is raised, considerations of energy become less important, and those of entropy become more important. Thus the miscibility increases with temperature. There are, however, a few systems in which the mutual solubility decreases with rising temperature and which are completely miscible only below a lower critical solution temperature (L.C.S.T.). Such systems are strongly hydrogen-bonded and, almost always, water is one of the two components. The energy of interaction of a pair of molecules in these systems depends strongly on their mutual orientation. At low temperatures a sufficiently high proportion of neighbouring molecules are able to adopt the orientations of low energy for the liquids to be miscible. These favourable alignments are broken up when the temperature is raised, and complete miscibility ends at a L.C.S.T.

It is the object of this paper to describe a second class of systems in which L.C.S.T. are observed, but in which the mutual orientations of the molecules are not of great importance. Ethane is completely miscible with ethanol, n-propanol and n-butanol at 25°C, but Kuenen and Robson[1] showed in 1899 that two liquid phases are formed in each of these systems over a small range of temperature near the critical point of pure ethane. *Figure 1* shows schematically two projections of the phase diagram of one of these systems. It is seen that the range of liquid immiscibility is small. It is bounded below by the L.C.S.T. and above by a critical point at which the gas phase and the liquid phase rich in ethane become identical. An increase of pressure raises the L.C.S.T. and increases the critical mole fraction of the alcohol. This line ends eventually at the gas–liquid critical point of the pure alcohol. These systems differ in two respects from the better-known class of L.C.S.T. First, only one of the components is polar, and not both, and secondly, the immiscibility is confined to a short range of temperature

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close to the critical point of the more volatile component. A few other systems which resemble these three have been discovered in the last sixty years: carbon dioxide (T_c 31°C) + *o*-nitrophenol[2, 3] (liquids immiscible at 26–40°C); carbon dioxide + nitrobenzene[4] (30–40°C); ethylene (T_c 9°C) + *p*-dichlorobenzene[5] (26·0–26·5°C); ethane (T_c 32°C) + 1,3,5-trichlorobenzene[6] (40·3–46·8°C); and propane (T_c 97°C) with many long-chain organic acids and esters[7].

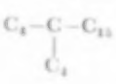
In some of these systems the L.C.S.T. lies above the critical point of the volatile component. In every system the less volatile component is either polar or of a different chemical type from the volatile component. However, it seemed to us that this polarity or chemical difference was not an essential feature of such systems, and we have therefore examined a range of hydrocarbon mixtures. Our starting point was the observation[8, 9] that the addition of propane to lubricating oils, which is made in order to precipitate the asphalt, sometimes gives rise to two liquid hydrocarbon layers if the temperature is above 70°C. Our first studies were therefore of solutions in propane of a series of pure liquid hydrocarbons with between 24 and 37 carbon atoms.

EXPERIMENTAL

Seven hydrocarbons, chosen, from those most readily available, for their large molar volumes and low melting points, were used as solutes.

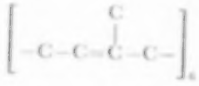
I n-octadecylcyclohexane (m.p. 40°C) $C_{24}H_{48}$

II 5-n-butyleicosane (m.p. < 0°C) $C_{24}H_{50}$

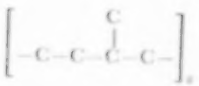


III 11-cyclohexylmethylenicosane (m.p. − 4°C) $C_{27}H_{54}$

IV Squalene (m.p. < 0°C) $C_{30}H_{50}$

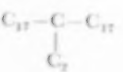


V Squalane (m.p. < 0°C) $C_{30}H_{62}$



VI 11-n-decyldocosane (m.p. 1°C) $C_{32}H_{66}$

VII 18-ethylpentatriacontane (m.p. 28°C) $C_{37}H_{76}$



Hydrocarbons I and II were supplied by the British Petroleum Company and were stated to contain less than 1 per cent impurity. III and VI were supplied by the American Petroleum Institute Research Project 42 as pure

VOL. 2 1961

samples sealed in nitrogen. IV was purified from 90 per cent squalene by passing a 3 per cent solution in petroleum ether through a Grade H alumina column. The infra-red spectrum was free from OH and CO bonds. V was prepared by D. Mangaraj by reducing the purified IV with hydrogen at 100 atm over a platinum-black catalyst. The infra-red spectrum was free from C=C bonds. VII was prepared from stearic acid. This was converted into stearone[10] by heating with iron filings at 300°C. The stearone was converted into a Grignard compound (with ethyl magnesium iodide) which was hydrolysed to the alcohol by ethanol. The alcohol was dehydrated with tolyl-*p*-sulphonic acid to give an unsaturated hydrocarbon which was finally reduced to VII by hydrogen with a catalyst of platinum black. The hydrocarbon was passed through a column of Grade H alumina. The infra-red spectrum was free from OH and C=C bonds. The melting point was 27·5°C.

Propane and ethane were supplied by the National Chemical Laboratory and had purities between 99·93 and 99·98 per cent.

Solutions were made in " Veridia " precision-bore glass tubes of 2·00 mm internal diameter and 9 mm external diameter. The lower end was sealed to give an internally square end. The involatile component was added first and weighed in air. The second component was added by distillation *in vacuo*; the tube was then sealed and re-weighed. The density of the mixture was calculated from the length of tube, with a small correction for the conical shape of the final seal. A water thermostat was used at 0–35°C and a vapour thermostat at 35–150°C. The tubes were shaken occasionally and the phase changes were observed with a travelling microscope.

RESULTS

Hydrocarbons II, III and VII were dissolved in propane to give mixtures in which the weight fraction of the heavy component was between 0·1 and 0·6. The specific volumes of the mixtures were varied between 4 cm³/g and 12 cm³/g and the temperature between 20° and 150°C. No liquid–liquid phase separation was found in any of the tubes.

All seven hydrocarbons were dissolved separately in ethane to give mixtures in which the weight fraction of the heavy component was between 0·01 and 0·5. The specific volumes and the temperature were varied between 1 and 5 cm³/g and 0° and 35°C. Every system was found to have a L.C.S.T. and a gas–liquid critical point of the type shown in *Figure 1*. The critical temperatures are listed in *Table 1*.

Table 1

System	*L.C.S.T.* (°C)	*Gas–liquid C.T.* (°C)
Ethane	—	32·3
Ethane + I	< 17	33·4
Ethane + II	27·7	34·5
Ethane + III	13·4	33·4
Ethane + IV	3·7	33·3
Ethane + V	22·6	33·6
Ethane + VI	10·6	32·6
Ethane + VII	< 15	32·5

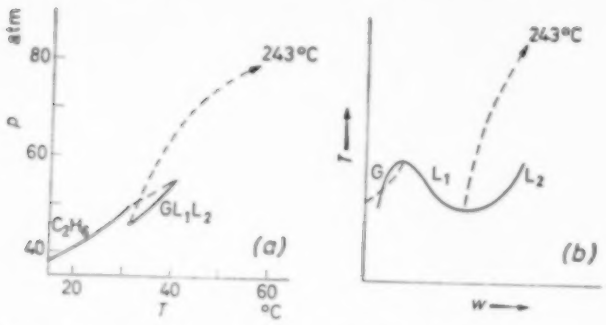


Figure 1. Graphs of pressure (p) and temperature (T) and of temperature and weight fraction (w) for ethane + ethanol: — vapour pressures and compositions of the univariant systems; - - - critical states of the mixtures; L_1 and L_2, the liquid phases rich and weak in ethane, respectively. Graph (b) is not to scale

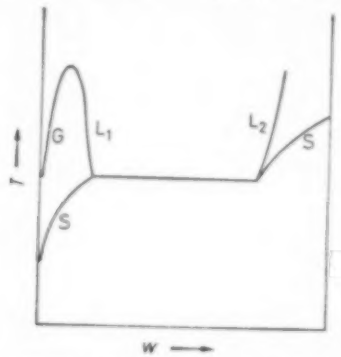


Figure 2. Graph of temperature (T) as a function of weight fraction (w) for a system in which the L.C.S.T. is not realized because of the solidification of the involatile component

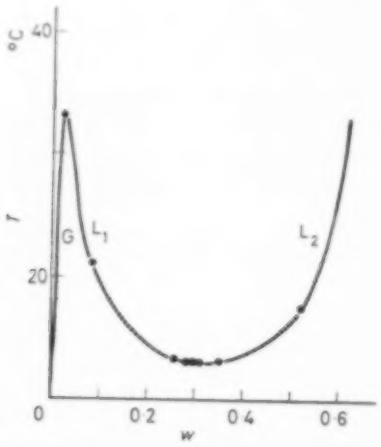


Figure 3. The (T,w) graph of ethane + hydrocarbon III. The critical point of pure ethane is at 32·3°C

VOL. 2 1961

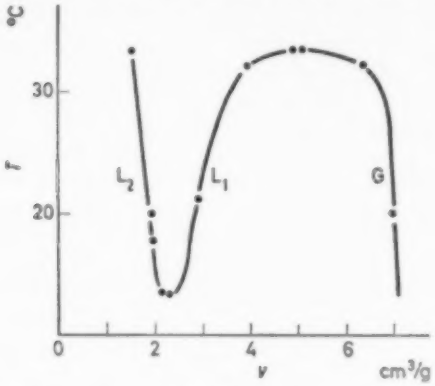


Figure 4. The graph of temperature (T) and specific volume (v) for ethane + hydrocarbon III

Two of the systems could not be cooled to the L.C.S.T. as the heavy component solidified. Here the temperature of the quadruple point (solid + liquid + liquid + gas) is shown as an upper limit of the L.C.S.T. The phase diagrams of these two systems are shown schematically in *Figure 2.* One system, ethane + III, was studied in greater detail than the others in order to establish beyond doubt that the phase behaviour is of the type shown in *Figure 1. Figure 3* shows the (T,w) and *Figure 4* the (v,T) projections of the (v,T,w) surface. They confirm that the system is of the type shown in *Figure 1.*

DISCUSSION

The results obtained here establish beyond doubt that this type of immiscibility is found even in mixtures of non-polar molecules of the same chemical type if the molecular sizes and energies of interaction of the two components are very different. The immiscibility is clearly caused by the approach of the volatile component to its own critical point.

A comparison of the results for the hydrocarbons without rings or double bonds, II, V, VI and VII, shows that the greater the number of carbon atoms in the heavier component the lower are both the L.C.S.T. and the gas–liquid critical temperature. That is, the larger the heavy component, the less is its miscibility with liquid ethane and the less its solubility in the critical phase of ethane. This low solubility in the critical phase leads to gas–liquid critical temperatures that differ little from that of pure ethane. It is probable that all paraffin hydrocarbons below about C_{20} are miscible in all proportions with liquid ethane at all temperatures up to the gas–liquid critical point of the mixture. It is known from the work of Kay[11] that this is so for hydrocarbons up to C_7. The results above show that the first paraffin hydrocarbon that is immiscible with propane must lie above C_{37}.

A comparison of I with II and of III with V shows that hydrocarbons with saturated rings (" naphthenic hydrocarbons " to the petroleum chemist) are less miscible with ethane than those without rings. A comparison of

IV with V shows that an unsaturated hydrocarbon is considerably less miscible than the corresponding saturated hydrocarbon. Roof and Crawford[12] have shown recently that isobutane and phenanthrene are immiscible in the liquid phase at 101°C. They have not studied the change of miscibility with temperature but have shown that the system has an upper critical solution pressure at this temperature. Their (p,w) section appears to be that of a system of the type shown in *Figure 1*. This temperature is 34°C below the critical temperature of pure isobutane, and so their results suggest that aromatic hydrocarbons are even less miscible with light paraffin hydrocarbons than are cycloparaffins or ethenes. This is in agreement with the known thermodynamic properties of more conventional systems[13]. The original work of Kuenen and Robson[1] shows that the miscibility of polar substances is even less than that of an aromatic hydrocarbon.

Gunst, Diepen and Scheffer[5, 14] have studied the phase diagram of ethylene with each of the following hydrocarbons: n-octacosane ($C_{28}H_{58}$), n-hexatriacontane ($C_{36}H_{74}$), diphenyl, naphthalene, anthracene, stilbene and hexamethylbenzene. In every case the melting point of the heavy component is too far above the critical temperature of ethylene (9°C) for liquid phases to be formed, but the course of the gas–liquid critical lines in (p,T,w) space suggests that the liquids would be immiscible were it not for the solidification of the heavy component.

Finally, we have shown that this type of immiscibility is very widespread in polymer solutions. Almost all solutions of high hydrocarbon polymers in solvents such as n-pentane, n-hexane and cyclohexane separate into two phases on heating above the normal boiling point of the solvent. This work has been published separately[15].

We wish to thank Dr D. Mangaraj, Mr J. C. Gardner, the British Petroleum Company, and the American Petroleum Institute Research Project 42 for the gifts of hydrocarbons.

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VOL. 2 1961

RECENT REDETERMINATIONS OF THE PHASE DIAGRAM OF THE SYSTEM: TRIETHYLAMINE + WATER

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Liquid mixtures which exhibit a lower critical solution temperature are of two types. The first type contains liquid pairs in which there is a great difference in molecular size between the two components[1]. The second, and by far the larger, group contains those in which interaction between the components occurs by means of a hydrogen bond. Triethylamine + water falls into the second group.

The system triethylamine + water has been very widely studied, the earliest work having been done in 1884. Since then a number of determinations of the phase diagram has been made, but later work has only been distinguished by the large number of different results that has been obtained. In *Figure 1* several earlier diagrams are illustrated.

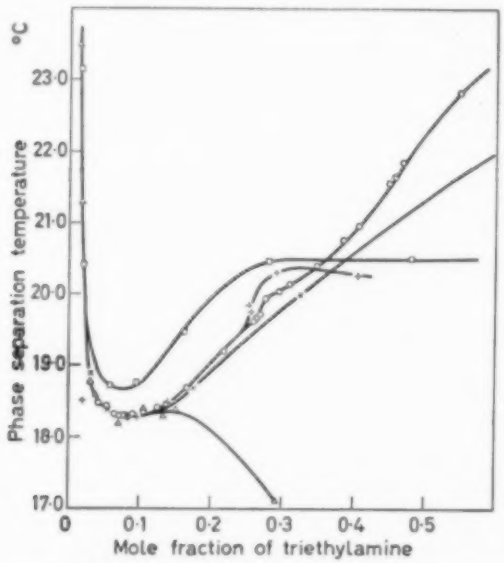

Figure 1. Previous results for the system: triethylamine + water: △ Guthrie[2]; □ Rothmund[3]; × Roberts and Mayer[4]; + Copp[5]; ○ Counsell[6]

It is well known that the exact shape of a phase diagram is a sensitive criterion of the purity of the materials used. It therefore seems likely that the variety of results can be traced to lack of attention to the purity of the samples.

In recent years a number of redeterminations of the phase diagram has been made and, while the general shape has become clear, it seems of interest to redetermine it so as to eliminate any final points of doubt.

It has been noticed by previous workers that, even after rigorous purification of the components and sealing of the samples under vacuum in glass ampoules, the phase separation temperature decreases with time. In *Figure 2* are shown the results with a set of initially pure samples sealed *in vacuo* in "Pyrex" glass by J. F. C. and re-examined eighteen months later by R. J. M. The lowering of the phase separation temperature was probably caused by solution of the glass of the sample tube, leading to the introduction of a small quantity of silicate ion which in turn affected the phase diagram.

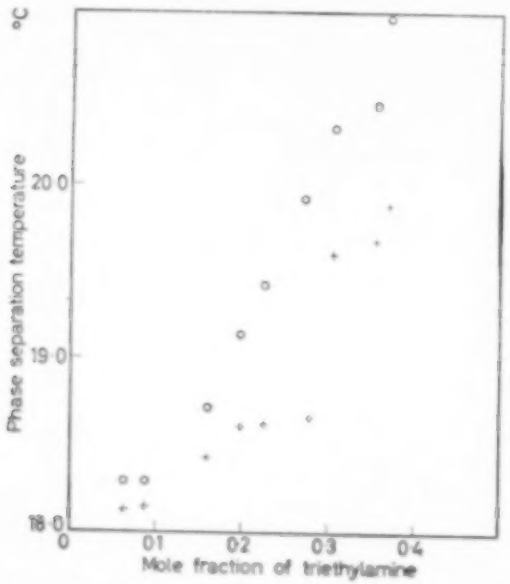

Figure 2. ○ initial results (J. F. C.); + results with same samples 18 months later (R. J. M.)

The most recent determination of the phase diagram has been made using composite tubes of "Pyrex" and silica glass. However, the phase separation temperature still exhibited a small time dependence. This, it was felt, could be traced to contact of the vapour phase and the "Pyrex" glass of the upper half of the sample tube. In view of these facts, our latest samples have been prepared in all-silica tubes.

EXPERIMENTAL

Materials

The triethylamine was high purity material obtained from B.D.H. and contained small quantities of lower amines. The material was refluxed with *p*-toluenesulphonyl chloride and potassium hydroxide to remove primary and secondary amines. The colourless amine was then fractionated from metallic sodium under a reflux ratio of approximately 15 : 1.

Following Copp[5], the fractions accepted from the final distillate were those for which the corrected condensation temperature at the still head was t°C, where t is given by $(t - 89{\cdot}50) = 0{\cdot}042\ (P - 760)$, P the atmospheric pressure in turn being corrected to standard conditions. The temperature at the still head could be controlled to $\pm 0{\cdot}01$°C.

The water used in all experiments was conductivity water with a specific conductance of $4 \times 10^{-7}\ \Omega$ cm.

The samples were prepared by distilling weighed quantities of the liquids into the silica sample tube under high vacuum. Before the final distillation into the sample tube, the liquids were degassed by frequent melting and freezing under vacuum. The sample tube was cleaned with chromic acid, nitric acid and distilled water, then baked out at 400°C for twelve hours.

The phase separation temperature of a sample was found by placing the silica tube, attached to the bulb of a large mercury-in-glass calorimeter thermometer, inside an unsilvered Dewar vessel, which in turn stood in a large thermostat. Both the Dewar and thermostat were fitted with efficient stirrers. By a judicious selection of the temperature in the thermostat, it was possible to raise the temperature in the Dewar at the rate of 0·1°C an hour. The observation of the phase separation temperature presented no particular problems. The phase separation temperature was taken as that at which the first heterogeneity appeared in the sample.

In order to minimize any effects due to contact between the sample and the silica vessel, the phase separation temperature was determined as shortly after the sample's preparation as possible. In retrospect this precaution seems to have been unnecessary as the phase diagram determined 18 months later with the same samples showed a maximum fall of 0·08°C in the phase separation temperature at the highest amine concentration.

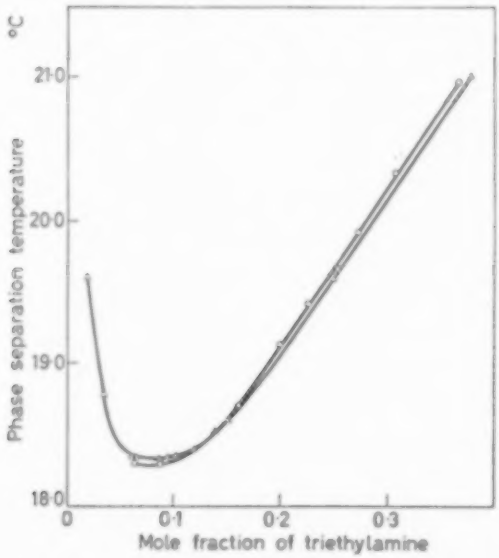

Figure 3. △ Kohler and Rice[9]; ○ present work

RESULTS

In *Figure 3* the results of the present work are compared with those of Kohler and Rice[7]. The agreement with the work of Kohler and Rice is very satisfactory.

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SECTION OF PHYSICAL CHEMISTRY

COMMISSION ON CHEMICAL THERMODYNAMICS*

RESOLUTION ON PUBLICATION OF CALORIMETRIC AND THERMODYNAMIC DATA

In 1953 the 8th Calorimetry Conference adopted a resolution outlining minimum publication standards for the guidance of authors, editors, and referees of calorimetric papers. Because this resolution has helped improve the quality of such papers, the 14th Conference (1959) authorized the preparation of a revised resolution on publication that would be more consistent with the expanded scope of the Conference and the present state of calorimetric science. The revised and expanded resolution that follows was adopted by the 15th Conference at Gatlinburg, Tennessee, 7–10 September, 1960.

VOL. 2 961

INTRODUCTION

This resolution is addressed not only to the specialist in calorimetry and chemical thermodynamics but also to those who determine and publish thermodynamic data as a subordinate part of their research. We urge all who publish thermodynamic data, for whatever purpose determined, to consider the suggestions to follow, so that maximum benefits from their work may be realized. We also recommend this resolution to journal editors and referees as a set of carefully considered criteria for judging the completeness and acceptability of papers reporting calorimetric data.

GENERAL PHILOSOPHY

The very nature of chemical thermodynamics imposes special burdens on the author of a paper reporting the results of calorimetric investigations. Because the body of thermodynamic data is highly interdependent, he must give enough information about his experiments to allow others to appraise the precision and accuracy of his results for proper consolidation with the existing body of data. Further, as accepted values of physical constants change, or as new thermodynamic data for related systems become available, later investigators often can recalculate results based on good calorimetry, however old it may be. For these reasons, an author's first responsibility is to report his results in a form related as closely to experimentally observed quantities as is practical, with enough details of the experiments and

* F. D. Rossini, President (U.S.A.), K. Schaefer, Secretary (German Federal Republic), J. Coops (Netherlands), D. M. Newitt (U.K.), K. S. Pitzer (U.S.A.), H. A. Skinner (U.K.), B. Vodar (France), G. Waddington (U.S.A.).

auxiliary information to characterize the results completely. For the convenience of the reader, the author should interpret and correlate the primary data, as appropriate, and present derived data in a form easy to use. However, derived or secondary data should *never* be published at the cost of omitting the primary data on which they are based.

NECESSARY AUXILIARY INFORMATION

Detailed auxiliary information is required to characterize the results of any definitive thermodynamic study. Applicable items listed in the following paragraphs should always be given either in full or by reference to accessible earlier publications containing full details.

Apparatus and procedures

A complete description of the apparatus and procedures, including details of the reaction container or calorimeter vessel, the controlled environment, and the temperature and time measuring systems; the method of calibration and the sensitivity of measuring instruments such as thermometers, bridges and potentiometers, timing devices, and flow meters; the method of determining the energy equivalent of, or otherwise calibrating, the system; the observational procedure; the method of data reduction; and the precision and accuracy of the results obtained, preferably established by using recognized reference substances such as the Calorimetry Conference samples of n-heptane, benzoic acid, and aluminium oxide for heat capacity or enthalpy measurements, or standard benzoic acid for combustion measurements.

Materials

The source of and/or method of preparing all materials used, including calibration, reference, and auxiliary substances; experimental values for analyses and pertinent physical properties of materials, and criteria of purity; and method of storing samples and preparing them for calorimetric measurements, if important.

Auxiliary data

Atomic or molecular weights; fundamental physical constants; temperature scales; units of energy and relationship between units; and values of thermochemical or thermodynamic data taken from the literature, with sources. The absolute joule or the defined thermochemical calorie equal to 4·184 absolute joules exactly and the International Temperature Scale, with the definition 0° Celsius (International) = 273·15° Kelvin (International), are recommended.

PRESENTATION OF RESULTS

It is not practical to give detailed recommendations for presenting the results of all kinds of thermochemical or thermodynamic investigations. However, the following paragraphs give recommendations for some important kinds of thermodynamic studies and will serve as guides for others.

VOL 2 1961

Thermochemical data

The following experimental data should be included if applicable: Energy equivalent of the calorimetric system; mass of sample and/or mass of product used in determining the amount of reaction; masses of auxiliary substances; corrected temperature increment; total observed energy change; ignition energy; chemical and physical specification of the initial and final states of the reaction; conversion to " standard " concentrations; corrections for side reactions; allowances for energy changes due to flow of gases, stirring, or other effects; allowances for energy from auxiliary substances; reduction to standard states, such as the " Washburn corrections "; temperature of experiments; and final experimental heat of reaction and uncertainty interval, with the chemical reaction to which the result applies.

Thermal data

The following information is considered indispensable for delineating the temperature dependence of thermodynamic properties of non-reacting systems, ascertaining the influence of thermal history on measured properties, and evaluating the precision of the results: A table of experimental values of heat capacity or enthalpy increment; the actual temperature increments used in the measurements when important (e.g., in transition, pre-melting, or anomalous regions), either explicitly or implicitly by chronological presentation of data or by a general statement; indication of values adjusted for curvature or pre-melting; values of the heat and temperature of essentially isothermal phase changes; and an estimate of the accuracy uncertainty of the results. These primary experimental data should be supplemented, but never supplanted, by a tabulation of smoothed values of thermodynamic properties at selected temperatures. Where applicable, such tabulations should include values of the Gibbs free energy function $(F - H_0^\circ)/T$, enthalpy (heat content) function, $(H - H_0^\circ)/T$, entropy, S, heat capacity, C_p (or $C_{\text{satd.}}$), and enthalpy, $H - H_0^\circ$ at 5° intervals from 0° to 50°K, 10° intervals from 50° to 300°K or slightly higher temperatures, and 50° to 100° intervals at higher temperatures, with appropriately smaller intervals in regions of thermal anomaly. Values at the two important reference temperatures, 273·15° and 298·15°K, and at the temperatures of phase changes should be included in the tabulations. Graphical or analytical representation of the results is sometimes worthwhile for the convenience of the reader, but such representations are seldom a satisfactory substitute for tabular presentation of accurate experimental results.

Calculated thermodynamic functions

As the usefulness of calorimetric data is often extended by giving calculated thermodynamic functions based on them, recommendations for presenting this kind of thermodynamic data are included here. The following information, with sources, is needed to characterize the results of statistical thermodynamic calculations: Details of the molecular model used, including bond distances and angles, specification of the exact conformation, moments of inertia or rotational constants, and symmetry number; complete vibrational assignment; parameters used for calculating

contributions of internal rotation, anharmonicity, centrifugal distortion, *etc.*; citation, usually by reference, of formulae and special tabulations used; comparison with experimental thermodynamic data, when available; and tables of thermodynamic functions at selected temperatures. The functions tabulated should include all of the following: the Gibbs free energy function, $(F^\circ - H_0^\circ)/T$; enthalpy (heat content) function, $(H^\circ - H_0^\circ)/T$; entropy, S°; heat capacity, C_p°; and enthalpy, $(H^\circ - H_0^\circ)$. In addition, values of enthalpy of formation, ΔH_f°, the Gibbs free energy of formation, ΔF_f°, and the common logarithm of the equilibrium constant of formation, $\log_{10} K_f$, may be published, if warranted. The values should be reported at temperatures so spaced that no serious loss of accuracy will result by interpolation with a formula equivalent to 5-point Lagrangian interpolation; for example, at 50° intervals to 300°K, 100° intervals to 1500°K, 200° intervals to 2500°K, and 500° intervals at higher temperatures. Values should also be tabulated at the reference temperatures, 273·15° and 298·15°K.

Non-definitive data

This resolution is concerned primarily with the publication of precise and accurate data taken by definitive techniques, but rough measurements are often made for technical purposes and these data occasionally are submitted for publication. As such measurements are sometimes made on materials of undefined composition or by techniques substantially inferior to those accepted as definitive, they clearly do not merit space in scientific journals on the same basis as definitive studies, and the foregoing recommendations do not apply in full. The same is true of calculated thermodynamic functions which are based on unsubstantiated or estimated molecular data and which are not verified by comparison with experimental thermodynamic data. However, even rough data or calculated values *may* be better than empirical estimates and thus have some value, but they are of doubtful significance as a basis for many theoretical deductions or for incorporation in critical tables of scientific data. Therefore, it is recommended that minimum journal space be allotted to such results and that the presentation clearly recognize their lack of reliability. The use of the American Documentation Institute Supplement may be appropriate for the bulk of such data, with the location attested only by a brief Note in a journal.

Note on symbols and terms

The symbols and terms used herein are simply those used by most American chemists, and their use in this report is not to be construed as a recommendation of the Calorimetry Conference. Two differences from European usage are:

(i) the superscript ° is used to designate the thermodynamic standard reference state;

(ii) the symbol F is defined as H — TS.

The I.U.P.A.C. Commission on Physicochemical Symbols and Terminology is expected to make recommendations soon, regarding these matters.

17th October, 1960.

VOL. 2 1961

OL.
2
61

VOL.
2
1961

SECTION OF ORGANIC CHEMISTRY*

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VOL.
2
1961

THE IMPACT OF STUDIES OF NATURAL PRODUCTS ON CHEMICAL INDUSTRY

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I regard it as a great honour to be able to speak to you at this opening ceremony of the Symposium on The Chemistry of Natural Products. I would like to express my sincere and heartfelt thanks to the Australian Academy of Science, and especially to the Organizing Committee, for the invitation which they extended to me and which I accepted with great pleasure.

This is my first visit to Australia, and I am delighted to have the opportunity of becoming personally acquainted with your country, for I have heard so many pleasant and charming things about Australia and its people.

Until recently, Australian economic life was confined mainly to agriculture. Now it has entered a new phase, and far-reaching industrialization is developing rapidly. That may well be one of the reasons why the Organizing Committee invited me, as a man who has studied natural products for fifty years and who has been manufacturing some of them on an industrial scale for forty years, to illustrate the chemistry of natural products more from the practical, that is, from the industrial side. In this short address I can give only a few examples from an immensely large field, for almost the entire organic chemical industry originated in the study of natural products.

One of the oldest branches of this industry, dating back one hundred years, is the dyestuffs industry. Until the middle of the nineteenth century, indigo and alizarin, both of vegetable origin, were the most important materials used for the dyeing of textile fibres. Baeyer worked for decades to elucidate the chemical constitution of indigo. In 1878 he achieved the first synthesis of indigo, but we know from another synthesis which he carried out subsequently that the process involved was wasteful. In 1890, Heumann of Zurich performed the first technically usable synthesis of indigo, based on the work of Baeyer.

A similar course of events was followed in the case of the other important natural dyestuff, alizarin, the chemical constitution of which was elucidated by two pupils of Baeyer in 1868. These two young chemists, Graebe and Liebermann, also succeeded in synthesizing alizarin.

Even the first artificial dyestuff, mauveine, which was prepared in 1856 by the extremely gifted chemist Perkin when he was seventeen years old, owes its origin indirectly to a natural substance. Perkin's teacher, Hoffmann, of the Royal College of Chemistry, suggested to him that he should attempt to synthesize quinine, which was highly valued because of its beneficial effects on malaria. In his preliminary studies Perkin discovered mauveine. This provided a basis for the world-wide development of the dyestuffs

industry; the greatest stimulus was, of course, given to the so-called " benzol chemistry ", and this engaged the interest of most chemists until well into the twentieth century.

At that time, investigations on natural products played a minor rôle, even though the profound investigations of Fischer and his school on proteins and the amino-acids from which proteins are built up, and on carbohydrates, were of great scientific importance. These investigations did not find any direct industrial application. They must be regarded, together with investigations on natural rubber, as important preliminary work that has since become of major significance to industry, namely for the manufacture of high polymers in the synthetic fibre and plastics industries of today, which have developed on such a colossal scale.

A new era in the study of natural substances was initiated early in this century by the investigations of Willstätter and his school on chlorophyll. Although chlorophyll, the colouring matter of leaves, had long been known to research workers, and its fundamental importance in the conversion of carbon dioxide in the air into organic substances under the influence of light was realized, the investigations on this widespread and important colouring matter did not lead to clear-cut results until Willstätter began his studies, for the usual chemical methods of investigations produced profound changes in the chlorophyll molecule. As long as the chlorophyll in leaves (like the blood pigment in haemoglobin) is bound to high-molecular-weight substances such as proteins, it is perfectly stable and resistant to light and to weak acids, but these can easily destroy the dyestuff dissolved out from leaves. Alkalis, oxygen from the air, and even enzymes induce changes in the chlorophyll molecule.

Chlorophyll plays a very minor rôle in industry, but it was from chlorophyll that we learned and developed many of the methods necessary for the preparation of highly sensitive substances, for chemical changes in chlorophyll could be easily observed with the naked eye or with the spectroscope. A further complication in the investigations on chlorophyll was the fact that the leaf colouring matter is not a uniform substance but consists of two yellow components, carotene and xanthophyll, and two green components, chlorophyll *a* and chlorophyll *b*. The two chlorophylls are very similar in composition and properties. It was not possible to use chemical methods to separate them because of the risk of decomposition. Only with the aid of physical methods, *e.g.* chromatography—as used first in 1912 by Tswett—or separation between non-miscible organic solvents, was it possible to obtain the pure components, chlorophyll *a* and chlorophyll *b*; the latter procedure was later developed systematically and led to Craig's counter-current apparatus.

From this example of chlorophyll, we learned how to purify and isolate sensitive natural products by means of physical methods and without using chemicals, not only on a laboratory scale but also on an industrial scale. The studies on chlorophyll revealed that enzymes may occur in living cells which break down, to some extent, the natural products which one is looking for. Thus chlorophyll is broken down by chlorophyllase, an enzyme which splits off the phytol ester group if chlorophyll is slowly extracted with an organic solvent.

VOL. 2 1961

The observations made during the study of chlorophyll proved of great assistance to us in the isolation of the cardiac glycosides. We were able to recognize that enzymes were splitting off sugars from the native glycosides during the extraction processes. This cleavage could be prevented if we wanted to isolate the glycosides in their native state. Alternatively, it enabled us to subject the latter to controlled, step-wise enzymatic degradation.

In his investigations on chlorophyll, and later on anthocyanins and enzymes, Willstätter followed a principle of his teacher, Baeyer. He writes about this in his autobiography[1] and reports that Baeyer said: "What are the distinguishing features of the great scientist? He should not govern but listen, he should adapt himself to what is heard and re-model himself on it. . . . This is what the old empiricists did: they lent an ear to Nature. The modern scientist does the same and I have also tried to do it. A very special influence is exerted on men when they approach nature. They develop quite differently from someone who approaches nature with a preconceived idea." Willstätter himself remarked: "In these words Baeyer associates himself with Francis Bacon's view that Nature is not to be governed except through obeying her."

The chemistry of natural products and its industrial exploitation underwent an expansion that could hardly have been foreseen, following the research work carried out on hormones, vitamins and antibiotics in the nineteen-thirties and nineteen-forties.

Hormones are the products of internal secretion glands, and are carried in the blood to the effector organs where they exert the most diverse effects. With the exception of a few very simple hormones such as adrenalin and serotonin, hormones are generally complicated substances. The great majority, such as the adrenocortical hormones and the sex hormones, are derived from steroids and can be prepared, on a technical scale, from readily available substances by chemical treatment, by partial or total synthesis.

Many other hormones such as insulin, oxytocin and vasopressin are polypeptides. The composition and the structure of insulin, the anti-diabetic hormone, have been elucidated by the brilliant work of Sanger. The total synthesis of insulin, which consists of fifty-one amino-acids arranged in two parallel chains, has not yet been effected. In preparing insulin today we are still dependent on the pancreas for our starting material. Nevertheless, it has proved possible to synthesize on an industrial scale simpler polypeptide hormones, such as oxytocin and vasopressin, which consist of eight amino-acids arranged in a ring.

The chemistry of the vitamins forms one comprehensive chapter within that of the natural products. Vitamins are so-called additives to nutrition, which are indispensable factors for growth and the normal metabolism of human and animal organs. As long ago as the beginning of the twentieth century they were considered to be of vital importance, and were therefore given the name vitamins in 1911 by Funk. However, twenty years elapsed before they were isolated and their constitutional formulae were elucidated. In 1931, Karrer obtained a highly effective concentrate of Factor A and was able to determine the constitution of Vitamin A. This was the first determination of the chemical structure of any vitamin. In 1933, Haworth

and Reichstein synthesized Vitamin C. In 1935, Kuhn and Karrer synthesized lactoflavin (Vitamin B_2). In 1936, Williams synthesized aneurin (Vitamin B_1). In the same year, Brockmann isolated Factor D, the anti-rachitic factor, and ascertained that it was identical with a cholesterol derivative obtained by Windaus at almost the same time.

Subsequently, whole series of vitamins were elucidated. Kuhn succeeded in synthesizing lactoflavin-5-phosphoric acid, which combined with Warburg's protein components to form the fully effective "yellow enzyme". This provided proof that a vitamin acts as a prosthetic group of an enzyme.

Only in the last decade has it proved possible to elucidate the structure of the important anti-anaemic principle, Vitamin B_{12}. This was prepared in a crystalline form almost simultaneously in England and in the United States in 1948. More detailed investigations were then carried out by the Folkers group in the Merck organization and by Todd and his associates in the University of Cambridge. The main portion of the molecule has a porphyrin-like structure with cobalt, built in a complex bond. The formula was elucidated with the aid of X-ray studies performed in Hodgkin's laboratory at Oxford.

In view of the great importance of vitamins to human beings and to animals, it is not surprising that, with the exception of B_{12}, they are prepared on a large scale by total synthesis. The value of production of vitamins for the United States in 1958, announced recently by the Census Bureau, was 300 million dollars at manufacturers' level[2].

Production figures are even higher for the antibiotics. Biologists, biochemists and industrial chemists have been feverishly active in the last decades, an activity that has not previously been experienced in the field of organic chemistry. You know the story of the discovery of penicillin, the first antibiotic, by Fleming in 1929, and its isolation, associated with the first clinical trials, by Florey and Chain in Oxford some ten years later. The sulphonamides, which derive from purely synthetic dyestuffs chemistry, had already been successfully employed in the treatment of many infectious diseases, but with the coming of penicillin, a new era began in this important branch of medicine. A search was then made for further antibiotics, countless soil samples being studied for strains of fungi and bacteria. As a result, a great number of substances inhibiting the growth of pathogens were isolated. However, only a relatively small number met the requirements of high potency against pathogens and relative absence of toxicity. Some examples, in addition to penicillin, are streptomycin, its dihydro-derivative, and tetracycline.

The chemical structure of most antibiotics has been elucidated. They have been found to be relatively low-molecular-weight compounds, although in some instances they have a rather complicated structure. Consequently, even in those instances where synthesis has been effected on a laboratory scale, no attempts have been made to synthesize them on an industrial scale. This work is left to the skilful micro-organisms; a suitable composition of the nutrient substrates and favourable physical conditions, such as temperature and ventilation of the cultures, leads to optimum development of the antibiotics. The growth of the micro-organisms takes place in culture

VOL. 2 1961

tanks containing up to 400,000 litres, such as are used in the United States. The antibiotics are isolated in various ways from the cultures and then prepared in crystalline form.

The antibiotic sales of many pharmaceutical firms amount to as much as 50 per cent of the annual turnover. The United States production of antibiotics for human use in 1958—announced by the Census Bureau—amounted to 362 million dollars at manufacturers' level[2].

Antibiotics, vitamins and hormones are products of research in recent decades. By contrast, the use of medicinal plants is much older. These have been used by man for some thousands of years. Until the middle of the nineteenth century they were, with few exceptions, the only material available for treatment and prevention of diseases. Throughout the middle ages the *materia medica* of plant origin seemed to be far more important and more respectable than, for instance, surgery. They were subject to the very strict regulations of the medical faculties.

It was, therefore, a natural development at the beginning of the nineteenth century, when modern chemistry and pharmacy began to develop, to study medicinal plants. Sertürner recognized and isolated morphine, the hypnotic and anaesthetic principle of opium, in 1805. Subsequently a whole series of other plants was investigated to detect similar products. Some of them were found to be complicated organic compounds of a basic nature. In view of their alkaline properties, which are due to their nitrogen content, they were called alkaloids. Many of them were shown to be the actual therapeutic agents, *e.g.* quinine from *Cinchona* bark used in the treatment of malaria, atropine from *Atropa belladonna*, and many others.

In more recent times, reserpine has been obtained from *Rauwolfia serpentina*, and the curare alkaloids have been isolated from South American poisonous plants or plant juices which the natives use as arrow poisons. Not all alkaloids, and there are some hundreds of them, have proved to be useful drugs, but many have become so well established in the medical armoury that they are used every day by doctors.

Until well into the nineteenth century, the preparation of drugs from plants or animal organs was exclusively the responsibility of the pharmacist. At first, extracts, and later pure substances, were prepared on an ever-increasing scale as the demand grew; finally, they were prepared in small factories, and thus began research on the rational preparation and chemical elucidation of the active principles. It was realized that the active contents varied greatly with the quality, particularly with respect to the origin and storage of the raw material. Some active principles decompose on storage, so that the only way to provide the doctor with a reliable drug is to isolate the pure substance so that it can be dosed according to weight, thus excluding variations in effectiveness. Only when the pure material is available is it possible to carry out chemical analysis and elucidate the constitution; then synthesis can be attempted.

Many of the plant alkaloids which are of importance in medicine today are obtained from hundreds of tons of plant material, either growing wild or, more recently, specially cultivated. The beautiful, crystalline, pure substances are then processed to make tablets, oral solutions, syrups, ampoule solutions, *etc.*

The vegetable kingdom provides us not only with alkaloids but also with many other highly active substances, for example, the cardiac glycosides obtained from *Digitalis* species, the therapeutic effect of which was first recognized by the English doctor Withering in 1785. It was not until 1859 that the French pharmacist Nativelle succeeded in isolating one of these glycosides, " digitaline cristallisée ". Today there are a great number of such cardiac glycosides of plant origin. However, it was shown that all the cardiac glycosides obtained in crystalline form up to 1930 were actually products obtained by enzymatic cleavage of the native glycosides. Today, the original, native glycosides are prepared on a large scale in industry. Some are subjected to enzymatic cleavage. In view of the increasing importance of cardiovascular diseases, these preparations are becoming indispensable. A change-over has, therefore, been made to selecting plant strains which are rich in glycosides, and cultivating them on a large scale so that we are no longer dependent on the wild plants as a source of raw material. Earlier, similar attempts at cultivation were made on a large scale in Indonesia with respect to *Cinchona*. For instance, various species were crossed in order to obtain bark which was rich in quinine.

The preparation of drugs is therefore not only of industrial but also of agronomical interest.

The vegetable kingdom of Australia[3] and the neighbouring islands, particularly those in the tropics, certainly includes as yet unknown natural products which may be used for therapeutic and other purposes. Australian research workers have already been active, and with success, in this field. The lectures by Dr Price and by Dr Mathieson will certainly provide us with interesting data on this work.

In this connection, I would like to refer to the recent working-up of species of *Rauwolfia*. It was *Rauwolfia serpentina*, which is found particularly in India, that was used for centuries in folk medicine " for all the ills of man ".

It was used for epilepsy, insomnia and insanity.
It was prescribed for dysentery, diarrhoea and cholera.
It was considered valuable in headaches and blindness.
It was a standard treatment for a wide variety of fevers.
It was applied as an antidote for insect bites and snake bites.

This last indication, " an antidote for snake bites " was mentioned to me as late as 1952 in Madras. It may well be that the popular belief that *Rauwolfia* was a panacea was responsible for the medical schools' refraining from using this plant for such a long time. Nevertheless, in the 1930's, Indian doctors were able to establish beyond doubt that the powdered root of *Rauwolfia serpentina* can be used successfully in states of excitement and in hypertension. Attempts were made to find the active substances and a great number of alkaloids were isolated from the various species of *Rauwolfia*. Unfortunately, the first alkaloids isolated some thirty years ago by Siddiqui and Siddiqui: ajmaline, ajamalinine and ajmalicine, as well as serpentine

VOL. 2 1961

and serpentinine, possessed no interesting pharmacological properties. Some twenty years, therefore, elapsed before Schlittler and his associates succeeded in isolating three highly potent alkaloids. One of these, reserpine, is effective in states of excitement and high blood pressure in human beings when given in fractions of a milligram. The action of reserpine is hypotensive and sedative. Schlittler also succeeded in elucidating the chemical structure of reserpine and other *Rauwolfia* alkaloids. The quite recently reported synthesis of reserpine by Woodward is a brilliant achievement. Nevertheless, it is still more economical to obtain the alkaloids from the roots of *Rauwolfia* than to obtain them by synthesis. It is estimated that the value of the annual production of reserpine is 20 million dollars. Use is made not only of *Rauwolfia serpentina* from India but especially of *Rauwolfia vomitoria* from Africa and *Rauwolfia tetraphylla* from Central America.

To conclude my address, I would like to outline my personal experience of investigations in one particular field and its industrial exploitation.

When rye is flowering, the naked seed buds can be infected by filamentous spores from a fungus. Instead of the grains of rye you then have proliferations, which, when the rye is mature, project from the ears as dark-brown horn-shaped sclerotia. These are the mycelia of the fungus *Claviceps purpurea*, the form in which the fungus spends the winter in the ground. In the spring the sclerotia germinate and spores are formed which infect the rye.

The brown horn-shaped sclerotia are best collected before the rye is harvested. For centuries they were used in popular medicine under the name " Secale cornutum ". They were mentioned for the treatment of post-partum haemorrhage by the Frankfurt doctor Lonicerus in his herbal book published as long ago as 1582. It was not until Stearns, an American doctor, published in 1808 a paper entitled " Account of the Pulvis Parturiens, a Remedy for Quickening Child Birth ", that the drug was used in medical schools. The chemists then attempted to isolate the active principles but were unsuccessful for a long time. In 1875, the French pharmacist Tanret was able to isolate the first alkaloidal preparation, " ergotinine cristallisée ".

At the beginning of this century, Barger and Carr, and the Swiss pharmacist Kraft isolated ergotoxin, but this product was scarcely used in medicine. One reason for this was, as I shall show later, that the ergotoxin preparations were not uniform, their composition varying greatly. On the other hand it was known that the effectiveness of extracts from ergot was subject to extraordinary variations, depending on the origin and the age of the raw material and the decomposition of the active principles during storage. The use of weak or inactive ergot preparations could be disastrous in post-partum uterine atony. The first task, therefore, was to isolate the active principle in a pure form so that it could be dosed according to weight. This task was fundamentally completed in 1918, when it proved possible to isolate, in crystalline form, ergotamine, a highly active alkaloid. Soon the alkaloid was prepared on a technical scale. The experience gained in the studies of chlorophyll facilitated the isolation of the highly sensitive substance ergotamine. Subcutaneous injections of $\frac{1}{2}$ mg of ergotamine elicit a rapid and long-lasting contraction of the uterus, thus stopping life-endangering haemorrhage.

When the pure substance was available, it was possible to analyse it chemically and elucidate its structure, and to attempt synthesis. Actually no total synthesis has yet proved successful. We still have to rely on the production of the raw material by a fungus, as we did at a time when we knew nothing of the production of antibiotics by fungi.

When the pure substance ergotamine was available, it was possible to carry out reliable pharmacological and clinical trials. It was found that ergotamine exhibited to a marked degree the antagonism to adrenalin which Dale had detected with ergotoxi preparations at the beginning of this century. Ergotamine not only exerts a constrictor effect on smooth muscle fibres, *e.g.* of the uterus, but it also exerts a marked effect on the autonomic nervous system, a so-called sympathicolytic effect. In the course of time, it has been widely used in internal medicine and neurology, for instance in migraine, in gastro-intestinal atony, in thyrotoxicosis, nervous tachycardia and, in combination with belladonna and phenobarbitone, in the treatment of autonomic imbalance, *etc.*

Later, a whole series of active principles similar to ergotamine were isolated from ergot. For instance, ergosine was isolated by Smith and Timmis in 1936, and then alkaloids of the ergotoxin group, ergocristine, ergokryptine and ergocornine, thus showing that ergotoxin was a variable mixture. In 1935, a more simple, water-soluble alkaloid, ergometrine, was discovered in four laboratories in England, the United States and Switzerland. Ergometrine exerts a rapid but somewhat transient contractile effect on the uterus but does not have any significant effect on the autonomic nervous system.

Within the scope of this short address, it is not possible to go into detail on the investigations, which stretched over some decades, on the structural elucidation and partial synthesis of the ergot alkaloids. However, I must mention something that is also of industrial importance: by making modifications in the molecule it is possible to obtain substances with new pharmacological properties. In this connection I am thinking of a passage from Sir Alexander Todd's Nobel Prize address: " At Oxford I had the privilege of working on the anthocyanins and other natural colouring matters with Robert Robinson. It was from him that I learnt that synthesis is not merely a means of confirming a structure arrived at by degradative studies. Synthesis and degradation are complementary tools in structural work, and, properly used, synthesis can serve not only in the elucidation of structure, but can in many instances open up wider vistas regarding the significance and function of biologically important compounds."

The heterocyclic ring system of lysergic acid, which is common to all ergot alkaloids, contains a readily hydrogenated double bond. When hydrogen is added to this double bond by catalytic hydrogenation, all the ergot alkaloids lose almost entirely their contractile effects on smooth muscle. Ergometrine becomes inactive, but the alkaloids of the ergotamine and ergotoxin type, in which lysergic acid is associated with a polypeptide residue, exhibit more marked and pure effects on the autonomic nervous system. The sympathicolytic action is enhanced. The vasoconstrictor action is replaced by a vasodilator action which is of beneficial effect in peripheral and cerebral vascular disorders. One consequence is subjective

improvement in hypertension due to increased cerebral oxygen uptake, which may or may not be accompanied by a fall in blood pressure. This property is most pronounced in the case of the hydrogenated alkaloids of the ergotoxin group.

The structure of ergometrine is simpler than that of the other alkaloids. In ergometrine there is an amide-like linkage of lysergic acid with an amino-alcohol, aminopropanol. If the amino-alcohol is replaced by a diethylamide group we obtain one of the most potent substances known. Even one-thirtieth of a milligram taken by mouth elicits, after thirty minutes, marked mental changes, such as occur in schizophrenia, accompanied by hallucinations, *etc*. The extraordinarily violent effect of lysergic acid diethylamide (LSD-25) is an obstacle to the more widespread use of this substance in therapeutics. At the moment its use is confined to psychoanalysis.

The aminopropanol group in ergometrine can be replaced by aminobutanol. This leads to a methyl homologue of ergometrine with a markedly enhanced and longer-lasting contractile effect on the smooth muscle of the uterus.

On the other hand, if the hydrogen on the indole nitrogen of the lysergic acid moiety of ergometrine is replaced by a methyl group, we obtain the most potent antagonist of serotonin, a neurohumour normally occurring in the body. The therapeutic possibilities of this synthetic derivative have not yet been fully elucidated. Nevertheless, it has proved in some cases to be more potent than adrenocorticoid hormones.

The marked widening of the range in which the ergot alkaloids and their derivatives are used resulted in a significantly greater demand for the raw material, so much so that supplies were inadequate. A change-over therefore had to be made to the artificial infection of rye fields. This was initially done by hand, and later by special machines. In his book[4], Barger estimated the world consumption of ergot to be 100 tons. The requirements today for pure preparations are many times as great, even though we use raw materials with a higher alkaloid content and protect the sensitive substances against degradation.

In previous centuries and even until quite recently, ergot, appearing as a poisonous impurity in cereals, was often the cause of serious large-scale poisoning of the population. By means of exemplary co-operation between chemical, pharmacological and medical research, ergot has evolved as the essential basic material for the production of important drugs, and today it must be cultivated in order to satisfy the needs of the industry and medicine. An enemy of man has been transformed into a friend.

Studies of natural substances not only increase and deepen our scientific knowledge, but also provide a basis for a highly developed industry which provides countless people with their daily bread, and helps to raise living standards and to treat or prevent disease. In this way excellent services are rendered to humanity. One of the most noteworthy endeavours of scientific research is to give the benefits of its splendid achievements to ever wider circles of the world's population. The Symposium which begins here today will also assist these endeavours handsomely.

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VOL
2
1961

NATURAL PRODUCT CHEMISTRY—RETROSPECT AND PROSPECT

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As a part of this Symposium, with its specialist lectures and scientific communications in which the latest results in natural product research are being reported, it is my task—and a rather difficult one—to attempt a broad review of the field, to consider its development and its present status, and to attempt an estimate of its future. Natural product chemistry is essentially a part of organic chemistry, itself one of the most remarkable of all the sciences, and one which is usually regarded by the layman as one of the most abstruse and remote from everyday life and thought. This view, is, perhaps, based on its content of jargon and its use of abbreviated molecular formulae as a kind of hieroglyphic script. It is hard to believe, however, that a science can properly be described as abstruse which permeates almost every material aspect of modern civilization, which stands as the bridge linking the physical with the biological sciences, and which is perhaps the biggest of the sciences in its factual content and in the number of its adherents. Organic chemistry is, I believe, the most logical of the sciences, and in its history of little more than a hundred and fifty years it has suffered fewer theoretical upsets than other science. It is a remarkable fact that the whole towering edifice of modern organic chemistry rests essentially on three basic concepts propounded in the third quarter of the nineteenth century—the concept of fixed combining power or valence due to Frankland, the Kekulé–Couper theory of the tetravalency of carbon and the capacity of carbon atoms to join together into chains and rings, and the van't Hoff–Le Bel tetrahedral carbon atom which gave us stereochemistry. All of these concepts were purely empirical, but they have stood the test of time and, on them, the whole of the science rests; advances in theory have certainly occurred since they were enunciated, but these advances have been essentially refinements giving more precise meaning to them, and have in no way upset or destroyed their essential validity. I doubt whether the same could be said of any other science.

There have been two definitions of organic chemistry. Historically the first, due to Berzelius, was " the chemistry of substances found in living matter ". The second, commonly ascribed to Gmelin, first appeared about fifty years later, when more was known about the peculiarities of substances found in living matter, and was quite simply " the chemistry of the carbon compounds ". Each of these definitions has some validity, but neither is wholly satisfactory, since the first is too restricted and the second, in certain respects, too general. A very large number of the carbon compounds known today are of purely synthetic origin and do not, as far as we are aware, occur in living matter. But it is undoubtedly true that the study

of substances which are found in living organisms has provided most of the major stimuli to the advance of organic chemistry throughout its history, and there is every reason to believe that it will continue to do so. After all, it was Pasteur's work on the tartaric acids that paved the way for the theory of van't Hoff and Le Bel; the anthraquinone dyes stem from the work of Graebe and Liebermann on alizarin from madder root (and let us not forget that Perkin's famous mauve dye resulted from an attempt to synthesize quinine); and work on polymerization and plastic materials goes back to the work of Harries on natural rubber. Many other examples might be quoted: in current organic chemical literature one is struck by the prominence of the ideas associated with conformational analysis, developed notably by Hassel and Barton. It could be argued that this concept goes back to the theoretical work of Hückel on the fused-ring system of the decalins, and Hückel received the stimulus to that work from the studies of Windaus on isomerism among the sterols. The direct study of substances found in living matter or, more briefly, of natural products, is as old as chemistry itself. It has been evident in organic chemistry throughout its history, although it has only become a dominant feature of the science during the present century. Its rise to a position of dominance was relatively sudden, and it is interesting to consider why this was so.

VOL. 2 1961

The original impetus to natural product chemistry—and, indeed, the move to divide chemistry into inorganic and organic sections—undoubtedly came from medicine and the use of natural drugs in its practice, and was partly scientific and partly commercial in character. Already in the eighteenth century what we may describe as scientific medicine was under way and drugs, such as extracts of *Digitalis* and *Cinchona* were being used rationally; again in connection with medical work, the animal product cholesterol was isolated and described by Poulletier in 1780. First the pharmacists and then the chemists, actuated by curiosity or by the prospect of financial reward, began to busy themselves with the extraction and purification of natural drugs known to be of value, and to study their chemistry. But this turned out to be far from easy, and indeed the decision to put all such things into a separate section of the science to be called organic chemistry was little more than a confession that the natural products were different from, and much more complicated than, the inorganic substances of the mineral world. One thing soon became clear: the natural products were all compounds of carbon and contained few other elements beyond hydrogen, oxygen, and nitrogen; and until a lot more was known about carbon chemistry, both theoretically and practically, little progress was likely to be made. So it was that the nineteenth century saw relatively little progress in the natural products field, such progress as there was being largely confined to the last two decades of the century. First the general theory of organic chemistry was developed, and then the experimental methods necessary for structural elucidation and synthesis of organic compounds, these latter stemming in part from the development of the organic chemical industry, notably in Germany, towards the end of the nineteenth century. But let us not forget that it was from work aimed at natural products in the shape of colouring matters that the dyestuffs industry developed. Nor should one forget the continuous and often unrewarding

effort of the workers in the field of physiological chemistry in the second half of the nineteenth century—work which has provided a base-line for much more recent organic chemical studies, and which also gave birth to the now flourishing science of biochemistry. And here let me note in passing that organic chemistry and biochemistry are complementary, and indeed merge into one another in the natural products field, so that distinction between them is at times rather artificial.

One cannot, of course, put precise dates to changes in scientific patterns, but round about the beginning of the twentieth century natural product chemistry suddenly started to come into the forefront of organic chemistry. One reason for this was, no doubt, the appearance of some scientific giants in the field—Perkin, Willstätter, and Fischer, to mention but three. But there was, I think more to it than that. Organic chemistry had, by that time, progressed to a point where it had the experimental techniques and the background knowledge necessary to ensure real progress in the study of complex natural materials. Furthermore, the rise of the organic chemical industry and the growing outlets for new materials encouraged work on natural materials with the aim of producing synthetic analogues which might at once have their virtues and be free of their defects, just as the synthetic dyes had in many cases proved better than their natural counterparts. Finally, the steady development of scientific medicine and the opening up of tropical colonial territories by the major powers had provided a further stimulus to the search for new natural drugs and their synthetic analogues as well as to the study of bodily components, both normal and pathological. Be that as it may, the fact of the development of natural product chemistry is not in doubt and it became an increasingly prominent feature of organic chemistry during the first twenty-five or thirty years of this century. It was effectively during this period that the broad features of the essential oils were worked out by Perkin, Wallach, and others, that Willstätter's studies on chlorophyll and on the nature of enzymes were carried out, and Emil Fischer made his brilliant investigations into the proteins and carbohydrates and his preliminary foray into the realm of the nucleic acid components. Perkin and his brilliant pupils Thorpe, Simonsen, Haworth and Robinson greatly extended knowledge of terpenes, natural colouring matters, alkaloids and carbohydrates, the schools of Wieland and Windaus forged ahead in the study of steroids and bile acids, while Hans Fischer developed his monumental studies on the porphyrin pigments.

Not all of this work was crowned with success. To quote but two examples, Willstätter's work on chlorophyll and enzymes ran into acute difficulties and Fischer was halted in his protein work after a brilliant start. This was due essentially to imperfections in experimental technique. In natural product work the German saying " Jeder Fortschritt der Wissenschaft ist ein Fortschritt der Technik " applies in very large measure. It is, therefore, convenient at this point to recall how the advances of recent years have been conditioned and made possible by developments in method. The first major advance came undoubtedly through the development of reliable microanalytical methods by Pregl. The effect of Pregl's work was enormous, although it is at times rather overlooked. To be able to cut the amount of a scarce natural material needed for analysis by a factor of about twenty made

possible the exploitation of fields hitherto barred to the chemist. But microanalysis was only the first of the big improvements; later came the introduction of chromatography—first by adsorption on alumina, as developed by Kuhn and Brockmann in particular, then partition chromatography on paper, ion-exchange chromatography, and finally vapour or gas-phase chromatography. Alongside these came electrophoretic separation methods and many others which in sum made the exact study of the complex natural macromolecules—the polysaccharides, proteins, and nucleic acids—possible for the first time. Just as great an impact has been made by the physical methods of analysis which have become available to us from the late nineteen-twenties onwards. First came the application of ultra-violet spectroscopy to the study of structure. One of the pioneers in this field I would mention today—Sir Ian Heilbron, a friend of many of us here and a staunch believer in the International Union of Pure and Applied Chemistry, and whose recent death we so greatly regretted. Later came the application of infra-red spectroscopy to which Dr Thompson, who has been discussing it during our Symposium, has made notable contributions; and, even more recently, the new and powerful technique of nuclear magnetic resonance. Again, the development of X-ray and electron diffraction methods in the analysis of crystal structure has been of enormous service to natural product chemistry by providing, in some instances, almost a complete answer to baffling structural problems, as in the brilliant work of Hodgkin on vitamin B_{12}. Finally, the availability of isotopes, and especially radioisotopes, has opened entirely new vistas in the study of such problems as biosynthesis.

Natural product chemistry, like science in general, has tended to advance irregularly on a broad front during this century, and during each phase of its development there were always individual investigators who stood rather apart and who broke new ground, or saw possibilities not apparent to others at the time. For this reason it is difficult, particularly with such recent events, to put precise dates to changes in scientific patterns. But, in broad terms, it seems to me that for about the first twenty-five to thirty years of the century most organic chemists dealing with natural products were pre-occupied almost entirely with the structure of compounds, and paid relatively little attention to their function, which formed the main interest of the biochemists who were becoming increasingly prominent. This preoccupation with structure led, of course, to the development of a vast array of experimental methods for the structural study and for the synthesis of molecules, and our catalogue of types occurring in nature increased by leaps and bounds. This process did not, of course, stop in the nineteen-thirties—new methods still came forward and older ones were improved, so that today the organic chemist's methods of synthesis are so powerful that it might almost be said that, macromolecules apart, almost any natural product can in principle be synthesized—and, indeed, this would seem to be emphasized by the successful total synthesis of substances as complex as cholesterol and cortisone, the carotenes, strychnine, chlorophyll, and cozymase. But let us face the fact that, in the past, many people have looked to the natural products merely as suitable materials for exercising chemical ingenuity, rather in the way that one might tackle a difficult crossword puzzle. This kind of approach has doubtless increased our store of factual knowledge, but

VOL. 2 1961

I doubt myself whether it will nowadays lead to any major advances in science, however convenient it may remain from the standpoint of producing exercises for Ph.D. students, and whatever its commercial importance. It is certainly not in the van of progress today, and it has been dwindling in importance since about 1930.

It was about this time that a new interest began to appear, slowly at first and later with increasing rapidity—an interest in structure in relation to function among natural products. It is this which has brought organic chemistry much closer to biology than it has ever been before. Equally, of course, it has been the realization that function must increasingly be considered in relation to structure that has brought the biochemists closer to their organic chemical colleagues, to the considerable advantage of both. What brought about this change? In a sense, I believe it originated in the movement of biology, spurred on by biochemical work, away from purely taxonomic and descriptive studies. A major influence was exerted by the work on accessory food factors or vitamins. The study of nutritional problems by Eijkmann, Hopkins, McCollum, and others had reached, by the nineteen-twenties, a point at which it was realized that these mysterious vitamins could actually be isolated as chemical individuals capable of structural investigation and eventual synthesis. The opportunity was seized upon by the chemists, and with it the very similar opportunity presented by the sex hormones. Structures were worked out, and soon synthetic vitamins and, later, hormones became available. But it was inevitable that the chemists who entered this field should find themselves fascinated by the further problems which turned up: why and how do the vitamins and hormones act, and what is the secret of their specificity? And so the advancing front of the subject began to take a definite orientation towards the solution of biological problems.

Now, as I have said, one cannot put precise dates to changes in scientific patterns and, whatever effect the nutritional work on vitamins may have had in triggering off the change, the ground has been in some measure prepared by earlier events in natural product work, and had been in a sense foreshadowed by some of the ideas and interests of a few of the outstanding figures in the field. Of major significance in this respect were the ideas on biogenesis, based on the structural relationships between individual compounds in different groups of natural products. Although this attracted the attention of several workers, the greatest influence was that exerted by Sir Robert Robinson, whose rationalization of structural relations in the alkaloid field in terms of biogenesis from amino-acids, backed by his classical tropinone synthesis carried out at room temperature in dilute solution, had a profound effect on the general thinking of natural product chemists which has lasted to this day. And we should remember that it was through his interest in biogenetic considerations in the field of natural pigments that Sir Robert, in association with Lady Robinson, was drawn in the late 'twenties into genetic studies on varation in flower colour using anthocyanin pigments as his tools—another foretaste of things yet to come.

It would be difficult to exaggerate the importance of biogenetic theories in the development of structural work on natural products—especially the alkaloids, colouring matters, and the terpenoids—but it should be remem-

bered that these theories were essentially expressions of structural relationships and were not based upon any studies of biosynthesis. Biogenesis as used by the chemist is not the same as biosynthesis, and failure to appreciate this led many biologists to pay less attention to biogenetic theories than the latter deserved. Equally, of course, it led some chemists to exaggerate their biochemical significance. The importance of the Robinson tropinone synthesis lay in its demonstration to the chemist and the biochemist that complex molecules could be built up from simple ones, using types of reaction well known to the organic chemist and under the kind of conditions which might well obtain in plants. But it has always seemed to me that the pursuit of "synthesis under physiological conditions", which it undoubtedly stimulated, was a blind alley so long as it was not coupled closely to studies on biosynthesis. Such studies on biosynthesis were not, until quite recently, really feasible. One recalls, for example, the ingenious but unsuccessful efforts of Raistrick to elucidate biosynthetic processes in fungi. It was only when isotopes began to become available that rapid progress could be made, and we have in recent years seen enormous strides in the elucidation of biosynthetic mechanisms in micro-organisms, plants, and animals. The clarification of the biosynthesis of the terpenoids and steroids by Bloch, Cornforth, and Lynen, is one of the most beautiful pieces of work published in recent years, and it also provides a remarkable vindication of the use of biogenetic theories in considering structural relationships among natural products.

VOL. 2 1961

So far, I have given my picture of the development of natural product chemistry. It has, of course, been a very rough picture. It has contained very little detail and many interesting features have been omitted altogether. I have, for example, paid no attention in it to the fascinating attempts to develop a kind of chemical classification of plants according to their content of certain substances and to relate it to botanical classification. Early studies on these lines are found in the classical researches of Baker and Smith on the eucalypts here in Australia, and the investigations of Erdtman on conifer taxonomy provide a modern example of this fascinating type of study. But, despite these omissions, I think it is possible to summarize from my picture the reasons for the great importance of natural product research as a major factor both in the development of organic chemistry and of the organic chemical industry. In the first place, it has presented to chemists a stream of challenging problems, both in degradative and synthetic work; their solution has enormously enriched the range of experimental methods applicable over the whole science. Secondly, the study of natural drugs has, in turn, initiated the search for synthetic materials with similar or better medicinal value; on this has rested in large measure the spectacular development of the pharmaceutical industry. Thirdly, it has given impetus to other areas of organic chemical industry—dyes and plastics, to mention but two. And, finally, its development has brought chemistry closer and closer to biology and has, indeed, opened possible routes to the solution of many of its problems.

But what of its significance today? Is it still a developing field and will it retain its importance? My own answer to both questions is yes; the changing pattern of natural product chemistry is to be expected, but the

importance of the subject remains. I have already suggested that the older type of structural study applied to isolated plant products is no longer a spearhead in the advancement of the science, but this does not mean that it has everywhere lost its importance from a practical standpoint. We have seen in recent years the medical value and industrial stimulus provided by such a natural alkaloid as reserpine, isolated from plant material for long used in oriental folk-medicine. It is likely that still other substances with significant and valuable pharmacological properties remain to be isolated from plant materials, and that, incidentally, clues to some of them may still be found in the folk-medicine of primitive people. In particular, the rich and comparatively uninvestigated flora of South-East Asia and the Australian continent still require careful study, and it is gratifying to see that this is now being undertaken on a collaborative basis following the excellent start already made by Australia's chemists. The spectacular success of some antibiotics should not blind us to the possibility that interesting materials may still be found in the higher plants as well as in the fungi and bacteria.

I believe, however, that now and in the future, the real spearhead of the subject will lie in studies closely associated with biological investigations, in studies where questions of structure and function are closely linked. Difficult problems abound, many of them of economic importance, and all fascinating from the scientific standpoint. In the animal kingdom, the arthropoda have been relatively little studied by the chemist, partly because of their small size and the trouble associated with collection of material. But they differ in many ways from other types of animal, and, even from our present scanty knowledge of their hormones and their pigments, it is clear that a rich field of investigation lies waiting here. The whole problem of parasitism in plants and animals also lies open. Already, from investigations with nematodes of the *Heterodera* genus, with which I have myself been concerned, it is clear that the factors which make a parasite specific to one type of host are chemical in nature and, in some cases at least, of relatively low molecular weight. Clarification of such problems in parasitology could be of considerable importance in agriculture and forestry as well as in veterinary and human medicine, and they warrant the most serious attention.

It would be possible to provide many examples of such unexplored or partially explored fields, but I would mention here only the natural macromolecules as a further field—a field which includes as its most interesting members the carbohydrates, proteins and nucleic acids. For these macromolecular substances are the very stuff of life, and ultimately it is on progress in their chemical study that a real understanding of enzymology, of immunochemistry, of virology, and of the chemical basis of heredity will depend. These materials present a tremendous challenge to the organic chemist as well as to the biophysicist. For, without in any sense underestimating the vital importance of physical and physicochemical properties in determining the way in which molecules such as those of the nucleic acids behave in the cell, I believe that the chemist still has his contribution to make if we are to solve the problems of the self-replicating molecule and the information code which seems to reside in the natural nucleic acids and

which in some way controls the synthesis of specific proteins. But work in these fields is difficult, and it will demand the development of still more refined techniques of experimentation and probably the inclusion of others, hitherto more common in the biochemical field. The new techniques necessary will be found—of that I am sure—and, using them, the future natural products chemist will go forward into these new and exciting fields and will continue as in the past to contribute at once to the advancement of science and to the well-being of the human race.

VOL.
2
1961

AUSTRALIAN NATURAL PRODUCT RESEARCH

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At a meeting of this kind, a considerable proportion of the papers delivered will inevitably be concerned with work carried out in the host country. I have assumed, therefore, that the purpose of the Organizing Committee in inviting me to speak to you about Australian natural product chemistry was to provide a framework for the picture which these papers will present. To do this it will be necessary for me to tell you a little about the historical background.

We are told that, in 1788, the first year of European settlement in Australia, the essential oil of *Eucalyptus piperita* was distilled and used medicinally as a substitute for oil of peppermint. But it seems unlikely that the enterprise shown by those early settlers had any significant influence on the utilization or study of the country's plant products[1]. It was not until 1852 that the distillation of essential oils was investigated seriously, and was later placed on a commercial basis, by a man named Joseph Bosisto, who set up a still, only a few miles from here, outside Melbourne. It is not clear whether the credit for this action is due solely to Bosisto, because at about the same time a second, and very significant, character appeared on the scene. This was Ferdinand von Mueller, a German from Rostock, who became Government Botanist of Victoria in 1853 and made a magnificant contribution to the botanical exploration of Australia and to the systematic study and description of the Australian flora. Without attempting to allocate credit as between Bosisto and von Mueller, we can certainly date to this period the foundation of interest in the study of natural organic products of Australian origin. Both Bosisto and von Mueller, the one with interests mainly commercial, and the other academic, had been trained in pharmacy which, in those times, of course, was a near equivalent to organic chemistry. Both saw the potential of the novel Australian flora—at a time when medicine and industry relied much more directly on natural products than they do now—and both contributed substantially to its exploitation. Each achieved eminence in his own sphere. Bosisto not only founded a firm of oil distillers and pharmacists which operated for nearly one hundred years, but he played a leading part both in State government and in the development of the pharmaceutical profession in Victoria. He distilled the essential oils from at least twenty-six species, representing the families Myrtaceae, Labiatae and Rutaceae, and reported the yields of oils and certain of their physical and medicinal properties. von Mueller, of course, achieved a world reputation as a botanist, was made a Fellow of the Royal Society of London, was knighted by the Queen of England, and made a hereditary baron by the King of Wurtemberg.

The work of these two men was a starting point for the study of Australian natural product chemistry. Inevitably, their interests and enthusiasm were transmitted to others, and notably to J. H. Maiden, whose link with von Mueller is clear and well documented. The setting up of the eucalyptus oil industry drew attention to the potentialities of other kinds of natural products, and the need for a broader basis for investigation was the theme ably expounded and developed by Maiden. Maiden, the first curator of what is now the Museum of Applied Arts and Sciences in Sydney, was a botanist, but one with well-defined chemical interests. We owe a great deal to him, but his main claim to fame, I think, is that he provided the stimulus for much of the early organic chemical research carried out in this country by H. G. Smith.

Smith made a systematic examination of the essential oils of numerous species of Eucalypts, of a number of other Myrtaceae, and also of the pines of Australia—*Callitris*, *Araucaria* and related genera. His organic chemical work was begun in 1895, at a time when terpene chemistry, though advancing rapidly in the hands of Wallach, Wagner and others, was still more or less in its infancy. Smith's researches, carried out in collaboration with R. T. Baker, a botanist, achieved a remarkable correlation between the chemistry and morphology of the genus *Eucalyptus*. He was a pioneer, not only from the purely chemical point of view, in the study of the constituents of essential oils but also, with Baker, in the broader field of the relation between chemistry and taxonomy, to which Professor Erdtman, the present President of the Organic Chemistry Section of the International Union of Pure and Applied Chemistry, has so ably contributed.

VOL. 2 1961

When H. G. Smith began his work there was only one chair of chemistry in each of the then four Australian universities, but while he was still active an important step was taken by the University of Sydney which, in 1913, established a separate chair of organic chemistry. The first holder of this chair was a young Englishman, a very remarkable young man. He is still young, and I am very happy that he is with us today—Sir Robert Robinson. Robinson was very interested in Smith's work, and he collaborated with him and stimulated him as he has so many others; but, unfortunately for Australian chemistry, he did not stay long in Sydney. Robinson's immediate successor, John Read, assimilated from H. G. Smith an interest in essential oils which persisted long after he left Australia. In like manner, personal contacts initiated the particular chemical interests of many others, and the transmitted influence of these earlier chemists on present-day work can still be traced from colleague to colleague, and from teacher to student.

It is clear, therefore, that the first important steps in natural product chemistry in this country stemmed from the occurrence of numerous plant species of high essential oil content and the incentive for investigation that these oil-bearing species offered. It is not my purpose to review the chemical achievements of these investigations; suffice it to say that current interest in essential oils has a marked biological slant, and investigation hinges largely on recent advances in technique. Radiocarbon labelling has been made use of, for example by Birch[2], to investigate the biogenesis of essential oils. The development of gas chromatography has made possible very precise analysis of the oils, with the result that the study of inter-specific

relationships and varietal differences, such as were first made by Baker and Smith, can be placed on a much firmer basis. Likewise, studies of seasonal variation in the composition of essential oils and of variation according to the physiological age of the leaf can now be carried out on very small specimens with comparative simplicity. This, naturally enough, is the direction which the interests of H. G. Smith's successors at the Museum of Applied Arts and Sciences, notably H. H. G. McKern, have taken.

The volume of chemical work carried out in Australia (and, even more, overseas) on essential oils of Australian origin has been very great, but the economic significance of the industry was and is small, particularly when compared with that of the older-established pastoral industry. As time went on, the increasing attention given to improvement in the pastoral industry had its influence on chemistry, and one aim in the search for greater efficiency has been the elimination of losses due to the ingestion of plants poisonous to sheep, cattle and horses. An indication of the significance of such losses is to be seen in the publication of *The Poison Plants of New South Wales*[3] and, more recently, *The Toxic Plants of Western Australia*[4]. The preparation, no less than the publication, of Hurst's book was responsible for the examination of the toxic principles of a number of poisonous plants. The work of Finnemore on cyanogenetic glycosides was the first chemical outcome of such studies, and this was followed by the isolation of such substances as the unusual aliphatic azoxy-glycoside macrozamin[5] and, more recently, by the examination of the liver-damaging pyrrolizidine alkaloids. I shall have more to say about these later. Numerous poisonous species have been and are being examined, some of them not undesirable weeds but deliberately introduced pasture plants which have proved toxic in particular environments. The need for examining poisonous plants has constituted, therefore, a second factor promoting the study of natural products by organic chemists.

In the past fifteen or twenty years, there have been profound changes in the pattern of scientific research in this country. This has been due to several causes, an important one being the changing situation in the universities. Up to 1945, the amount of research work carried out in the chemistry departments of Australian universities was limited by small staffs, few research students and poor facilities. In the post-war period, university activities have expanded considerably, staffs have increased in size, research students in number, and despite the ever-present deficiencies there is a conspicuous improvement in research facilities. One result has been a considerable diversification of interests, and new fields of work have been tackled, some as a logical development from previous projects, others for reasons essentially the same as that of Sir Edmund Hillary for climbing Mount Everest—" because it is there ". As far as natural products are concerned, these new ventures, breaking right away from the traditional phytochemistry, may be exemplified by Professor Cavill's investigations of ant metabolites and by Dr Sutherland's examination of marine animal pigments.

A further stimulus to research has been provided by scientists coming to this country from overseas. Two such men who have made outstanding contributions to the chemistry of natural products are Lemberg, whose

work on the chemistry and biochemistry of porphyrins is too well-known to require any comment from me, and Gottschalk, likewise noted for his investigations of the sialic acids.

Another important factor has been the considerable expansion in governmental research, centred mainly as far as the subject of this Symposium is concerned, in the C.S.I.R.O. Chemical Research Laboratories. One field in which the Organic Chemistry Section of the Chemical Research Laboratories has been very active is the study of long-chain aliphatic compounds by Hatt, Murray and their colleagues. An outstanding feature of this work has been the level of instrumental development achieved by Murray which has made possible the separation of long-chain compounds in a high degree of purity, and also the deduction of structures following separation and identification of the components of complex mixtures of oxidation products. Hatt's group has made major contributions to the chemistry of wool wax and of sugar cane wax[6]; they have separated and identified the alcohols of carnauba wax, they have elucidated the structure of the novel nonadecenylhydroxycyclohexenones present in Tigaso oil from New Guinea[7], and are currently making considerable progress in the study of acetylenic compounds of local origin.

The phytochemical activities of the C.S.I.R.O. rank—after the early influence of essential oils and the latter one of stock poison problems—as the third major factor determining the development of natural product chemistry in this country. This influence has not been due primarily to the calibre of the scientific work in the C.S.I.R.O. laboratories, nor to its volume, but to a quite different cause. During the 1939–45 war, sources of certain of the more essential imported drugs of plant origin were sought in the native flora. Though not successful, this search made evident the need for a systematic survey of the pharmacological potential. So, in 1944, the C.S.I.R.O. Division of Plant Industry planned such a survey to involve botanical, pharmacological and chemical collaboration. With one or two exceptions, such as the hyoscine- and hyoscyamine-containing *Duboisia* species, background pharmacological information was almost negligible. The starting point of the programme, therefore, was a preliminary botanical survey in the hands of Dr L. J. Webb[8]. This soon revealed that the volume of chemical work would be far beyond the capacity of the chemists available, so the co-operation of the universities was sought, those interested in natural product chemistry were encouraged, problems were suggested to them, and plant materials provided for their work. After a few years the number of chemists involved and the volume of work in progress was such that the survey, with its initial botanical impetus, acquired more and more a chemical flavour, and eventually full responsibility for it was assumed by the Chemical Research Laboratories. Nevertheless, the corner-stone of all this phytochemical work was and is the botanist in the field, who explores, collects and supplies materials for those in the laboratory, and it is largely through the provision of this collecting facility that the C.S.I.R.O. has influenced directly and indirectly natural product chemistry in this country. I should make clear, of course, that by no means all plant chemistry is dependent on the C.S.I.R.O.—the very active group in Western Australia, for example, is entirely self-contained. However, an average of something

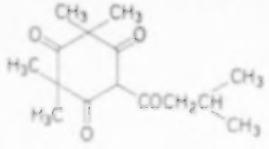
like 200 requested species are collected and distributed here and abroad each year, and about 30 per cent of the papers presented by Australian chemists at this Symposium are directly associated with the survey. A further aspect of the activities of the C.S.I.R.O. Chemical Research Laboratories is the part played in encouraging the fullest use of physical methods in structural organic chemical studies; for the purpose of this Symposium the most important facet of this is the X-ray crystallographic work of Dr Mathieson carried out in the Division of Chemical Physics.

The study of alkaloids was the initial objective of the C.S.I.R.O. programme, because alkaloids were believed to offer the most promising approach to pharmacologically useful materials, and it was to alkaloids also that the first university collaborators turned. But the broader the scope of the information that can be obtained concerning the native flora the better, and the provision of plant materials to those interested in them is not limited to species thought to be of potential economic interest. Apart from alkaloids, then, considerable attention has been paid to the study of triterpenes, notably at the Universities of New South Wales, Western Australia and Queensland, of cardiac glycosides, cyclitols, colouring matters, coumarins and so on. All these activities, hinging to a large extent on the centralized collection of plant material and involving periodical informal meetings of those interested, have come to be known as the phytochemical survey, and I shall subsequently refer to it as such.

This historical account, brief though it has necessarily been, leaves little opportunity for discussion of chemical work. To review the whole field would be quite impossible, so I have chosen to mention three recent topics, each representing one of the three factors influencing Australian natural product chemistry to which I have referred.

Firstly, essential oils: activity in essential oil chemistry since 1945 has lacked coherence as compared with earlier years. Although many have contributed, much of the effort has gone into clearing up long-standing problems, while the rest has been thinly spread over a wide field. From the somewhat heterogeneous results I will draw attention to one point only, namely the increasing number of phloroglucinol derivatives which have been isolated and identified as components of essential oils, usually predominantly terpenoid. Examples of such substances are leptospermone (I) and evodionol (II), and the more recently established angustifolionol (III), alloevodionol (IV) and torquatone (V). The major interest of these phloroglucinol derivatives lies in their association with Birch's development of the " acetate " hypothesis.

Secondly, the chemistry of plants toxic to livestock: in every country pastoralists suffer to a greater or lesser degree from losses caused by poisonous plants. The plants causing these losses are usually known or are soon recognized because of an obvious association between the ingestion of the plant and the onset of symptoms. However, this is not always so, and it is now appreciated that there are at least three groups of plants which can cause heavy loss of stock—and in some parts of the world, of human life—as much as two years after ingestion, so that recognition of the responsible species was not at first easy. The three groups of plants are the genus *Senecio* and some closely related species, certain members of the genus



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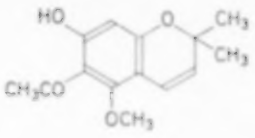

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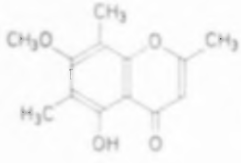

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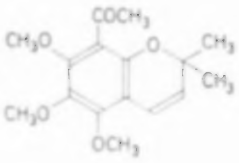

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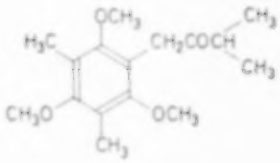


(V)

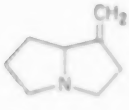
Crotalaria, and a number of members of the family Boraginaceae. All three groups contain the liver-damaging pyrrolizidine alkaloids with the chemistry of which the names of Adams and Menshikov are closely associated. Investigation of these alkaloids in this country was inspired by Dr L. B. Bull and his colleagues of the C.S.I.R.O. Division of Animal Health, following their recognition that toxaemic jaundice, a disease causing serious loss of sheep in southern New South Wales and northern Victoria, was associated with the grazing of *Heliotropium europaeum*[9]. Chemical work on this species was commenced in the C.S.I.R.O. Chemical Research Laboratories with the object of isolating the constituent alkaloids, determining their structures, and providing pure substances for biological study. This has developed into an extensive collaborative programme, different aspects of the mode of action of the pyrrolizidine alkaloids being under investigation in several laboratories. Thus, the pathological effects of the alkaloids on the liver are being examined by Bull and Dick[10], who have already carried out detailed studies of the relation of damage by the alkaloids to the storage of copper in the liver. Professor Christie of the University of Melbourne has investigated the action of the alkaloids on liver cell enzyme systems in the intact animal, a major biochemical effect being on the diphosphopyridine nucleotide-dependent enzymes[11]. The effects on nucleoprotein synthesis are being studied by Professor Morton in the University of Adelaide. Dr Gallagher of the McMaster Animal Health Laboratory, Sydney, has investigated the neuro-muscular blocking action of the alkaloids and confirmed *in vitro* the inhibition of enzyme systems requiring pyridine nucleotides[12]. He has observed the formation of copper complexes by certain of the alkaloids, a point of some interest in relation to the part which copper can play in the disease in the field.

Because of the effects on liver cell nuclei, Christie suggested to Professor Clark of the University of Tasmania that investigation of the mutagenic activity in *Drosophila* might be opportune. This suggestion led to the particularly interesting discovery that the pyrrolizidine alkaloids are

strongly mutagenic[13] and, furthermore, at a dose rate lower relative to the toxic dose level of other mutagens. Further studies in this direction are also under way in the Botany Department, University of Melbourne, and requests are also being received from biologists in other countries for supplies of alkaloids for the study of chromosome breakage and mutagenic action. From these collaborative studies, coupled with work elsewhere, there is accumulating a body of information concerning the structural features necessary for the liver-damaging activity of the alkaloids.

The prerequisite for all these biological programmes is the availability of the pure alkaloids and this, of course, is contingent upon the activities of the chemist. At the chemical level, but closely linked with the biological work, the metabolism of heliotrine *in vivo* is being studied by Mr Dann in the Division of Animal Health, at present with unlabelled alkaloids as a preliminary to the use of labelled heliotrine. On the purely chemical side, the work hinged initially on the elegant application by Culvenor[14] of partition chromatographic methods for isolating the alkaloids and, with many species, on the recognition (following earlier work by Russian chemists[15] and by Warren[16] in South Africa) of the importance of the *N*-oxides which sometimes constitute over 90 per cent of the total occurrence. Culvenor has made a preliminary examination of over eighty species of plants which are potential producers of pyrrolizidine bases, isolated many previously undescribed alkaloids and determined the structures of a number of them. As a result of the investigation of *Heliotropium europaeum*, the initial emphasis was on the Boraginaceae, which in general contains diester bases involving two esterifying acids, as compared with the more common macrocyclic diesters of dicarboxylic acids found in *Senecio* species. Of all this work, however, that which is probably of the widest academic interest has been concerned with a *Senecio* alkaloid, one of the longest-known pyrrolizidine alkaloids, jacobine. Jacobine was isolated by Barger[17] and others from *Senecio jacobea* or ragwort, which is responsible for stock losses in many parts of the world. Degradative studies were carried out in the C.S.I.R.O. laboratories by Bradbury[18], and from the results of these the main features of the structure were deduced by Geissman[19], then working temporarily in Melbourne. The complete stereochemical picture has now been revealed by X-ray crystallographic studies and will be discussed by Dr Mathieson.

Recently the emphasis in this pyrrolizidine field, on the chemical side, has shifted to the genus *Crotalaria*, several species of which are implicated in stock disease problems here and overseas. However, the main chemical interest is concentrated on the isolation of a number of unesterified bases, and these appear *not* to possess the power of causing liver damage. Examples of these are 1-methylenepyrrolizidine (VI), 7-hydroxy-1-methylenepyrrolizidine (VII) and 1-methoxymethyl-1,2-dehydropyrrolizidine[20] (VIII).



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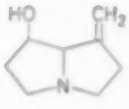

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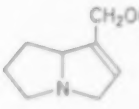


(VIII)

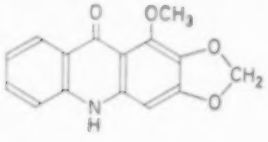
Table 1

	Quinolines	*Furoquinolines*	*Acridines*	*Quinazolines*	*Indoloquinazolines*	*Canthinones*	*Benzyl-iso-Quinolines*	*Imidazoles*
Sub-Family I RUTOIDEAE	Orixa Lunasia **Galipea** **Cusparia**	**Fagara** **Zanthoxylum** Evodia **Orixa** Melicope Lunasia Medicosma Haplophyllum Boenninghausenia **Dictamnus**	Evodia Melicope Haplophyllum		Zanthoxylum **Evodia**	Zanthoxylum Pentaceras	**Fagara** **Zanthoxylum** **Evodia**	**Pilocarpus**
Sub-Family III FLINDERSIOIDEAE	Flindersia	Flindersia **Chloroxylon**						
Sub-Family V TODDALIOIDEAE	Casimiroa	Balfourodendron Casimiroa Acronychia Hortia **Skimmia**	Acronychia		Hortia		**Phellodendron** **Toddalia**	Casimiroa
Sub-Family VI AURANTIOIDEAE		Glycosmis **Aegle**		Glycosmis Aegle				

VOL. 2 1961

My third example concerns the so-called phytochemical survey. As I mentioned previously, the objective of the C.S.I.R.O. survey was a search for alkaloids and this also became the starting point for a number of our university colleagues. For this reason more attention has been paid to the chemistry of alkaloids than to that of other types of plant constituents. Although no special emphasis has been placed on any one group of plants—except in so far as earlier work pointed to the likelihood of alkaloids being present—certain families have inevitably received more attention than others. One of these is the Rutaceae, a family which is widely distributed throughout the warmer parts of the globe. Taxonomic problems in the Rutaceae became evident very early in the survey, and as long ago as 1947 I had occasion to discuss with Dr L. J. Webb the possibility that, limited though they were, our chemical data might be of some value for taxonomic purposes. Despite the limitations, therefore, it seems to me worthwhile to illustrate some aspects of the phytochemical survey by examining the results in relation to what is known of the alkaloid pattern in the Rutaceae as a whole. I hope this will not only serve the primary purpose of the lecture, but will also stimulate others to fill in the numerous gaps in the chemistry of a most interesting group of plants.

From the point of view of alkaloid production, the Rutaceae are one of the most versatile of plant families. Dividing the alkaloids into arbitrary structural types there are now eight categories*, and data are available for



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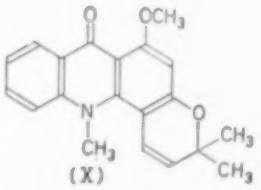
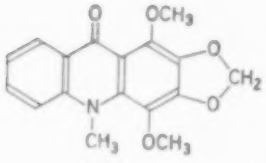


(X)



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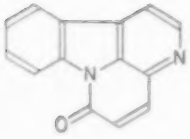

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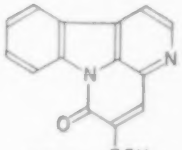

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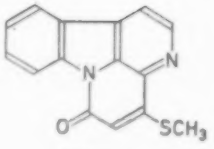


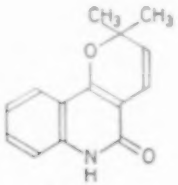
(XIV)

* Excluding the amides *N*-(2-*p*-anisylethyl)-*N*-methylcinnamamide, fagaramide, neoherculin and aegeline.

four of the seven sub-families listed by Engler and Prantl[21]. The remaining three sub-families are monogeneric and for our present purpose may be disregarded. The names printed in **bold** type in *Table 1* show the distribution of alkaloid-containing genera as it was known about 1946 when the programme in this country was getting under way.

Additions to these categories were soon made by the isolation and identification firstly of a number of acridine derivatives—5-acridones—exemplified by (IX), (X) and (XI), and shortly afterwards of three canthinone alkaloids, (XII), (XIII) and (XIV), the last having a methylthio-substituent[22]. Subsequently, Russian chemists have isolated from the rutaceous genus *Haplophyllum* what appears to be an acridine derivative[23], co-occurring, as in the Australian genera, with furoquinolines.

The structures of two novel types of quinoline derivative were established, a dimethylpyrano-2-quinolone (XV) from *Flindersia australis*[24] and the 2-phenyl-4-quinolone (XVI) from *Lunasia quercifolia*[22]. The latter was later isolated by Goodwin, Smith, Velasquez and Horning[25] from another *Lunasia* species, *L. amara*, and from *Casimiroa edulis* by Sondheimer[26].



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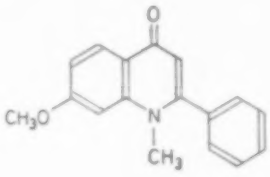
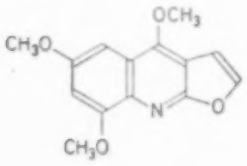


(XVI)

Less novelty, but much more variety, has been encountered among the furoquinoline group, initially represented by three alkaloids but now numbering at least fifteen, exclusive of several dihydrofuroquinolines[22, 27]. Examples are (XVII), (XVIII), (XIX) and (XX).



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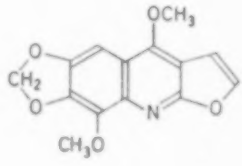
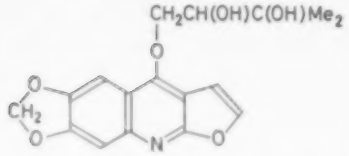


(XVIII)

Our knowledge of the alkaloid distribution in the Rutaceae has been supplemented considerably by these results and also, of course, by work elsewhere, of which I would mention particularly that on the quinazolines by our Indian colleagues, and on the furoquinolones by Japanese chemists. The present position is shown in *Table 1*.

Looking more closely at the information in this table, it is clear that in so far as any structural type might be regarded as characteristic of the Rutaceae

VOL. 2 1961



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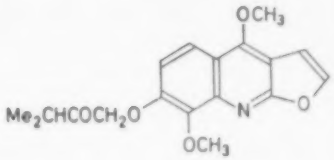
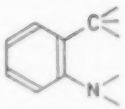


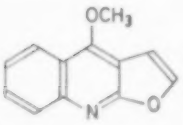
(XX)

it is the furoquinolines, which have not been reported from any other family*. But the acridines, likewise, are restricted to the Rutaceae and are always accompanied in the plant by furoquinolines; with certain exceptions, the quinoline alkaloids are confined to the Rutaceae and are often found together with furoquinolines, while in the genera containing quinazolines (*Glycosmis* and *Aegle*) furoquinolines are also present. It seems only reasonable, therefore, to regard these four as a biogenetically homogeneous group based formally on the " anthranilic acid " unit (**XXI**) common to all of them.



(XXI)

In addition to these four, we have the biogenetically distinct groups represented by the imidazoles, the benzylisoquinolines (themselves showing considerable structural variation) and indole derivatives, such as the canthinones, related to tryptophan. The versatility of the family becomes



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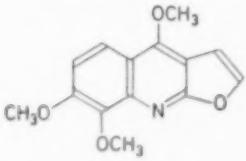

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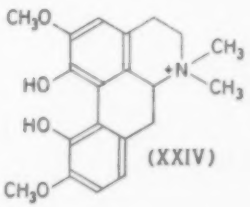

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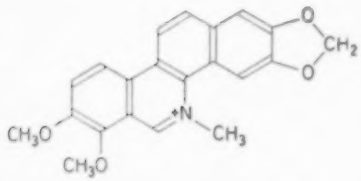

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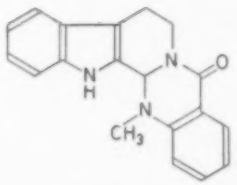


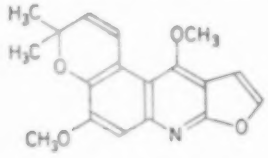
(XXVI)

* Since this paper was written, furoquinoline alkaloids have been reported from several additional rutaceous genera.

even more apparent when it is seen that not only are there certain genera, such as *Evodia*, capable of producing alkaloids by several of these biogenetic pathways, but an individual may make use of more than one route. Thus, from *Zanthoxylum ailanthoides*, Tomita and Ishii[28] isolated the furoquinolines dictamnine (XXII) and skimmianine (XXIII) and the quaternary aporphine magnoflorine (XXIV), while from *Zanthoxylum rhetsa*, Chatterjee, Bose and Ghosh[29] isolated chelerythrine (XXV) and three indoloquinazolines of which evodiamine (XXVI) is one.

Looked at against the complexity of the over-all metabolic picture, this versatility of alkaloid production is perhaps not especially surprising, but nevertheless it does distinguish the Rutaceae from other families and so deserves notice. It may suggest that the family is a rapidly evolving one, but, in any event, the data presented by the twenty-four genera so far known to contain alkaloids clearly make it desirable that as many as possible of the one hundred and twenty or so remaining genera be examined. Some, of course, have been examined without alkaloids being detected; others are known to produce alkaloids and work already in progress bears out the promise of much more interesting chemistry to come.

One further aspect of the chemistry of the Rutaceae warrants mention. Among the alkaloids to which I have referred have been several in which an isopentane unit is attached as an addendum to the type skeleton, for example, acronycine (X) in the acridine group, flindersine (XV) in the quinoline group and acronidine (XXVII) in the furoquinoline group, while there are several furoquinolines with isopentane ether substituents. There are in the Rutaceae numerous other examples of this kind, notably among the coumarins, representatives of which have been isolated from at least twelve rutaceous genera. Of those twelve genera, ten provide examples of courmarins involving the combination of one or more isopentane units. There are also a number of furocoumarins analogous to the furoquinolines. Among the flavanoids, recent examples are the flavanone isoprenoid ether



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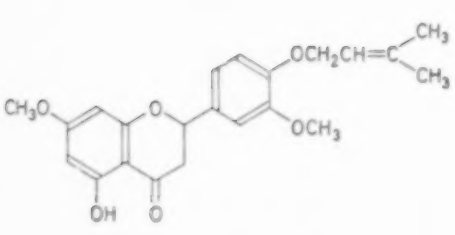

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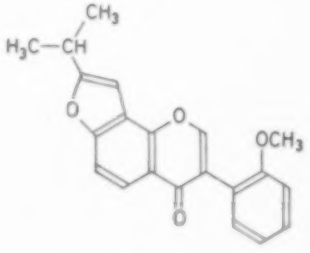
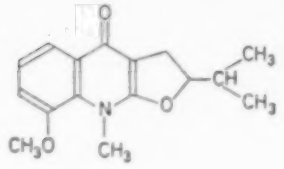


(XXIX)

VOL. 2 1961

(XXVIII) reported by Geissman[30] from *Evodia sarcocca* and the isoflavone munetone (XXIX) isolated from *Mundulea suberosa* by Dutta[31].

I have drawn attention to these substances, because this capacity to add an isopentane unit to a wide variety of molecular types is widespread through the Rutaceae and appears to be a biochemical characteristic of the family. It also gives rise to structural correlations which may have some biogenetic significance. For example, in the genus *Lunasia*, occurring together with simple furoquinolines, there are a number of isopropyldihydrofuroquinolines such as (XXX) and (XXXI), while *Orixa japonica* contains several



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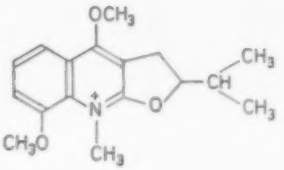

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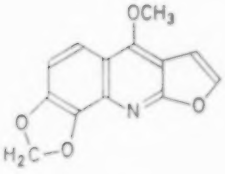

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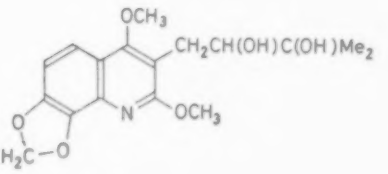

(XXXIII)

furoquinolines, such as kokusagine (XXXII), together with the alkaloid orixine which has recently been shown by Terasaka[32] to have the structure (XXXIII).

In his book *The Structural Relations of Natural Products*, Robinson[33] writes of the furoquinolines that there is no good clue to the origin of the furan group. He outlines three possibilities—that it is a residue of the tryptophan side chain, that it arises by degradation of an aromatic ring of the acridones, or that it is formed by condensation of a suitable intermediate with a 2,4-dihydroxyquinoline derivative. I should like to refer to a fourth possibility which I suggested in 1948 in a lecture to the Sydney University Chemical Society, namely, that the furan ring represents a degraded isopentane unit. Since that time, of course, the origin of the isopentane unit from acetate units has been established, and it may well be that the furan ring represents, as in Robinson's third suggestion, no more than union with one acetate unit. However, the more devious route remains a possibility which is not rendered any less probable by the co-occurrence of kokusagine and orixine—the loss of the isopropyl group by a retro-aldol change can so easily be visualized. This view, foreshadowed by Haworth[34], has also been put forward, and possible mechanisms have been discussed, by Birch[35] and Seshadri[36].

To sum up, the abundance of essential oil-bearing species in the Australian flora provided the background for the chemical work of H. G. Smith. But Smith could not and would not have achieved what he did without the botanist, R. T. Baker, and, behind him, J. H. Maiden. The importance of stock poisoning by plants led Finnemore and others to investigate their chemistry, but these investigations would not have gone far without the stimulus provided by the veterinary scientists. The current interest in plant chemistry associated with the C.S.I.R.O. phytochemical programme hinges on the initial botanical survey, on the pharmacological incentive for the study of alkaloids, and on the botanical collections. Likewise, the work of Gottschalk and of Lemberg undoubtedly owes much to its medical contacts and environment.

If a moral is to be drawn from the development of Australian natural product chemistry it is surely that the study of natural products flourishes best when there is the closest collaboration between chemist and biologist.

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VOL. 2 1961

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VOL.
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THE TOTAL SYNTHESIS OF CHLOROPHYLL*

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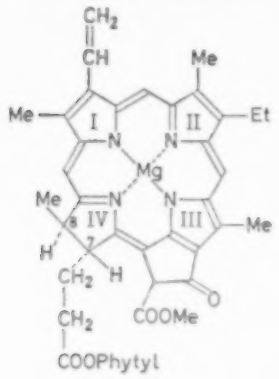
Chlorophyll *a*, the major green pigment of the plant world, is certainly the most widespread and conspicuous of organic natural products. Few can be unaware of its decorative function, and all are beneficiaries of its central role in transforming sunlight into substance and sustenance. Yet the fruitful chemical study of this green badge of life did not commence until fairly recent times. For chlorophyll *a* is a very reactive, sensitive, and complicated substance. Only when, early in this century, the genius of Willstätter applied itself to the problem, were the first sure steps taken. That great investigator isolated the pigment—and its closely related frequent minor concomitant chlorophyll *b* as well—in the pure state, established correctly the empirical formula of the substance, and laid down a sound and extensive preliminary basis of transformation and degradation. These achievements can be measured against the fact that the isolation of chlorophyll in a state of purity is even now, after more than fifty years, no mean feat, and, further, that the empirical formula defined by Willstätter, repeatedly called into question by subsequent investigators, has stood the test of time. For some period after this solid foundation had been laid by Willstätter there was little activity until three new groups took the field late in the 1920s. Stoll, who had played a prominent rôle in the early studies as a collaborator of Willstätter, took up the work anew, and made important contributions, as did Conant in the United States. But by far the greatest contribution was made by Hans Fischer and his collaborators at Munich. Fresh from his dramatic conquest of the blood pigment, Fischer hurled his legions into the attack on chlorophyll, and during a period of approximately fifteen years, built a monumental corpus of fact. As this chemical record, almost unique in its scope and depth, was constructed, the molecule was transformed and rent asunder in innumerable directions, and the fascination and intricacy of the chemistry of chlorophyll and its congeners was fully revealed. These massive contributions were crowned by the proposal, in 1940, of a structure which was complete except for stereochemical detail. Finally, in a series of elegant investigations completed only during the last few years, Linstead and his associates at Imperial College were able to solve the stereochemical problem and to provide definitive confirmatory detail in respect of the number and disposition of saturated carbon atoms within the nuclear framework. Half a century of structural study had culminated in the complete formula (I) for chlorophyll *a*[1, 8].

Our active interest in chlorophyll was initiated four years ago, in 1956. The first questions we asked were very general ones. The structural investigations had been carried out almost entirely during the twilight of the classical period of organic chemistry. Only the very simplest basic

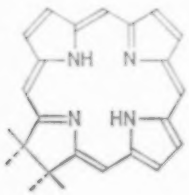
* A brief communication recording the results on which this lecture is based has appeared in *J. Am. Chem. Soc.*, **82**, 3800 (1960).



(I)

elements of theory played any role in the whole vast study. Neither was succour or control sought in chemical principle, nor was any attempt made to place the often striking observations in any generalized framework. Would the conclusions from such a study stand scrutiny from the viewpoint of the present day? Was the structure proposed for chlorophyll correct? When we embarked upon the examination of these questions, we entered a chemical fairyland, replete with remarkable transformations which provide unusual opportunities for the testing and further development of principle, and we cannot but urge others to follow us in penetrating what must have seemed to many the monolithic wall of a finished body of chemistry. But this is not the place to outline those opportunities at length. Here we shall mention only a few major points, which brought us at first to view the proposed structure for chlorophyll with considerable scepticism, and whose resolution was of importance in our subsequent planning.

Let us first consider an unusual feature of the structure (I), namely, the saturated carbon atoms at positions 7 and 8, with the attached, so-called " extra ", hydrogen atoms which give chlorophyll its position as a member of the general class of green substances known as chlorins (II). Chlorins in turn are derivatives of the simpler, more electronically symmetrical, fully aromatic red porphyrins (III). It is well known that simple chlorins, as might be expected, are readily oxidizable to porphyrins. Not so chlorophyll itself, and many of the chlorins derived from the plant pigment. Surprisingly,



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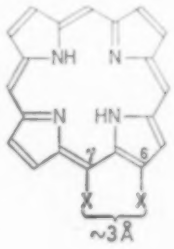
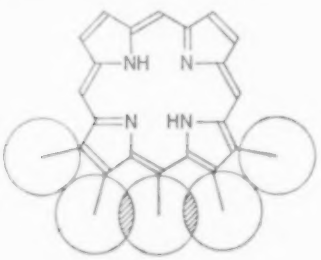


(III)

these substances are deprived of the extra hydrogen atoms only with considerable difficulty. A second point which claimed our attention was the presence in the structure (I) of the carbocyclic 5-membered ring fused to the pyrroloid ring III of the nucleus. While no direct measurements have been made of the atomic parameters of any porphyrin or chlorin, it is possible to surmise with some confidence that groups attached at the 6- and γ-positions of those nuclei will be at a remove of some 3 Å (see III). Consequently, the formation of a bond which joins substituents in those positions must involve considerable distortion, with much resultant strain. The presence of strained systems within the molecules of substances of natural origin need not, of course, present an occasion for surprise, and indeed chlorophyll undergoes very ready changes which are interpreted as involving the opening of the carbocyclic ring. But the ring can be closed again with much ease, particularly so in the porphyrin series. Finally, mention may be made of the fact that porphyrins and chlorins containing substituents at the γ-position, and a carboxyl group at C–6, lose carbon dioxide with ease, while, by contrast, the γ-unsubstituted analogues are resistant to decarboxylation. All of these observations baffled us for some time, until they received a very simple rationalization in terms of the principle that two things cannot take up the same space at the same time. Thus, the lower periphery of porphyrins derived from chlorophyll is heavily laden with substituents—so much so that there is not room for all of them without considerable distortion of bond angles or lengths (see IV). Consequently, all of these molecules will be strained. If now we examine the possibilities for



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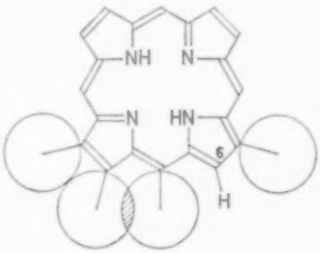
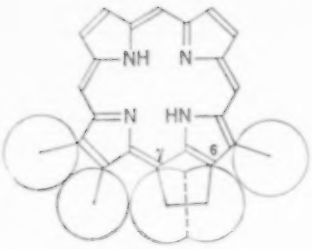


(V)

the relief of steric compressions in these systems, we find that the phenomena set down above are readily explicable. The ready decarboxylation of the highly substituted acids is a consequence of the extrusion of the elements of carbon dioxide from a site at which there is not enough room for them (see V), and the cyclization to 5-membered ring compounds may be viewed, in an unsophisticated but valid manner, as a process in which the atoms involved are literally pushed into union (see VI). Finally, it is clear that the removal of the hydrogen atoms from C–7 and C–8 of a chlorin substituted at those positions, accompanied, as it must be, by the transformation of those carbon atoms from the tetrahedral to the trigonal condition, will exacerbate steric compressions, particularly when the γ-position is also substituted. Conversely, we recognize that *there is a strong natural factor in such heavily substituted porphyrins which favours the transformation of trigonal*



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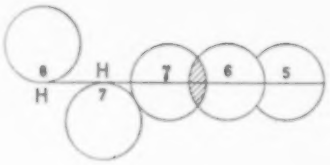
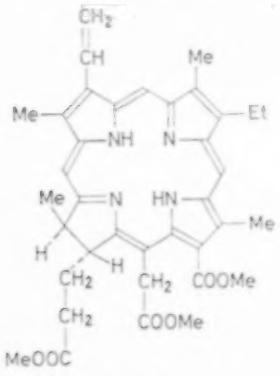


(VII)

peripheral atoms into tetrahedral ones (see VII). These simple but powerful considerations not only assuaged much of our doubt about the structure of chlorophyll, and permitted us to plan a synthetic attack with reasonable confidence that our objective had been correctly defined, but also provided the basis for our first major decision of policy. Thus, that portion of the chlorophyll molecule containing the extra hydrogen atoms must have seemed to any who might have contemplated the problem of synthesizing chlorophyll one of the most formidable obstacles to be surmounted. We decided that the inherent factors favouring the attainment of the saturated condition by C–7 and C–8 in heavily substituted porphyrins permitted us to pay little heed to that problem in the first stages of our investigation. We had in mind such possibilities as that hydrogen atoms, suitably coaxed, might well wander to the desired positions from another site in a suitably constructed porphyrin molecule. How far this general presumption was justified will become clear in the sequel. In any event, we turned our attention first to the development of a new porphyrin synthesis.

In order to define further our primary objective, we should point out at this time that, as is often the case in the study of complicated natural products, our problem had in some measure been simplified by earlier studies. The central magnesium atom of the chlorophyll molecule is easily removed by acids, and readily put back through the agency of basic magnesium halides. The phytol grouping of the molecule can be removed by hydrolysis, and



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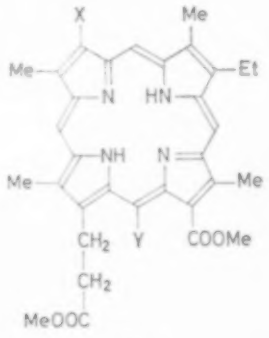
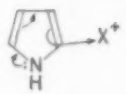


(IX)

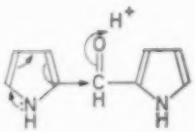
can be replaced smoothly, either by chemical or enzymatic means. Finally, the carbocyclic 5-membered ring can be cleaved or re-closed at will. That is to say, the product of all three changes—chlorin e_6 (trimethyl ester) (VIII), key substance in chlorophyll chemistry—can be converted into chlorophyll *a* itself by a short series of simple and well-known changes, and consequently it was chlorin e_6 which was our actual synthetic objective. The substitution pattern of the chlorin e_6 molecule is, to a considerable extent, simple, and led us to presume that we must devise a synthesis of a porphyrin of the structure (IX).

Now, the porphyrin syntheses of an earlier day, magnificent for their time, were most ill-suited to our purpose. Carried out under bold but brutal conditions, they led in almost all cases to very complicated mixtures of porphyrins, in small, frequently microscopic, yields. The structures of the substances produced could seldom be assigned with confidence on the



(X)

basis of a single synthesis, and the conditions were such that electronegative and other reactive substituents, and γ-substituents of any kind, survived only in part, if at all. By contrast, we required a method which would lead in high yield to a single product of known structure, containing substituent groups of variegated character—for we were well aware that we might have some distance to go after this primary objective had been achieved. The principle on which our projected method was based may be introduced through recollection of the great sensitivity of simple pyrroles to attack, at the α-position, by electron-deficient centres (see X, *arrows*). One of the best-known of such reactions is that in which a pyrrole with a free α-position



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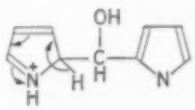

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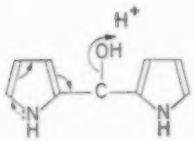

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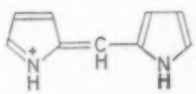
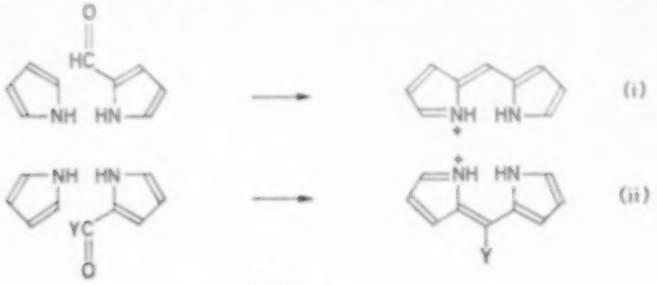


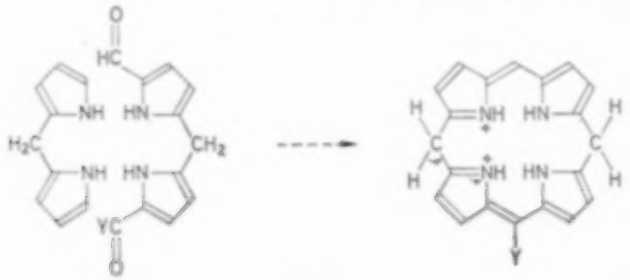
(XIV)

combines with a pyrrole α-aldehyde in the presence of acid to give a dipyrromethene (XI→XII→XIII→XIV). This combination takes place with extraordinary readiness—frequently it proceeds rapidly even at temperatures far below the freezing point—and although it is usually necessary to define the best conditions in any individual case by extensive experimentation, the reaction can ordinarily be coaxed into giving a fairly high yield of the condensation product. The reaction can be brought about not only with pyrrole aldehydes (XV, i), but also, with only somewhat greater difficulty, with pyrryl ketones (XV, ii). We supposed that, if the components in



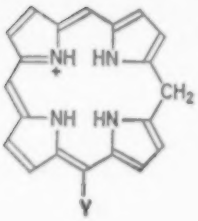
(XV)

these separate schemes could be united in pairs, a condensation between molecules so constructed might permit the ready elaboration of the ring system present in the porphyrins (see XVI). We realized that the double dipyrromethene system shown as the possible proximate product of such a



(XVI)

reaction was unlikely to remain as such, and considered that that doubly charged species might well readily lose a proton (XVI, *arrows*) to give a material containing the system (XVII), which should be capable of considerable charge resonance stabilization, with its single positive charge distributed over all four nitrogen atoms. Further, if such a cation were capable of tautomerization to (XVIII), we can foresee the possibility of the ready loss of an acetic acid chain from the γ-position (XVIII, *arrows*), with conversion of the nucleus to a fully aromatic porphyrin salt system (XIX). On these grounds we deemed it unwise to choose as our objective a porphyrin substituted in the γ-position by the acetic acid chain which chlorin e_6 contains in the corresponding position, and chose instead a β-propionic acid chain for that site; such a chain would not be susceptible to extrusion,



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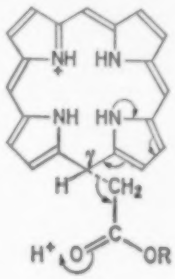
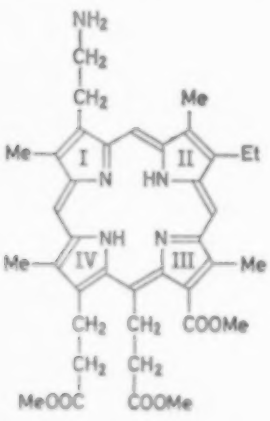


(XVIII)

(XIX)

it offered manifold possibilities for transformation to the acetic chain ultimately desired, and it seemed a plausible candidate for utility in chlorin-forming sequences. Further, we considered it unlikely that a highly reactive and sensitive vinyl group could be carried through any considerable sequence of reactions without complication, and chose as a precursor for such a group a β-aminoethyl function, the elimination of whose nitrogen at an appropriate stage might accomplish our objective. The porphyrin we desired to synthesize had now been fully specified as (XX), and it defined our basic building blocks, in the sense of the four relatively simple monocyclic pyrroles shown in (XXI). The preparation of these substances,



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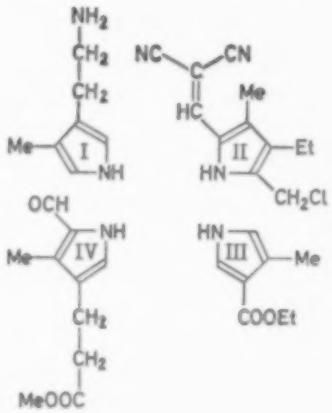
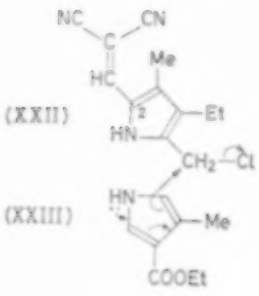
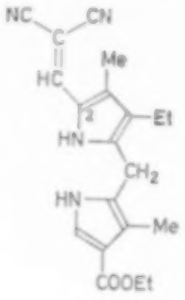


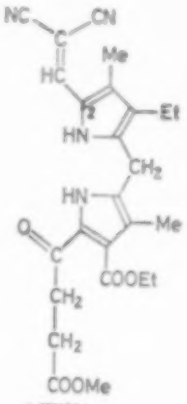
(XXI)

though arduous, need not concern us here; two were made by known methods[2], with some practical modifications, and the others were prepared from known compounds[3] through short new sequences. Once they were in hand, we proceeded to combine them in pairs. In the first instance, the dicyanovinyl compound (XXII) was condensed with the ring III component (XXIII) in hot aqueous ethanolic hydrochloric acid (see XXII and XXIII, *arrows*) to give the dipyrrylmethane (XXIV). It may be noted that 3-methyl-4-carbethoxypyrrole (XXIII) has two free α-positions, and





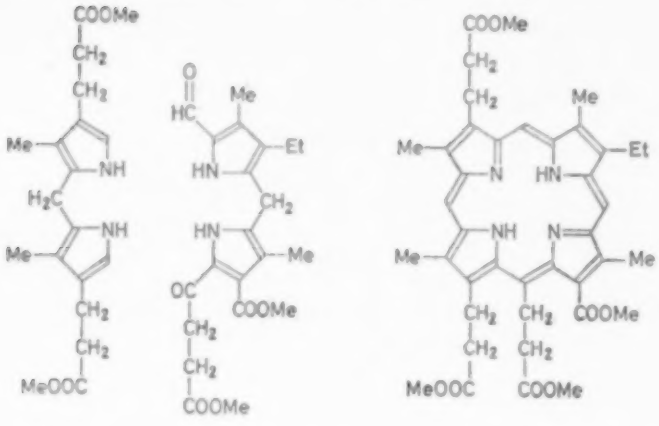
(XXIV)



(XXV)

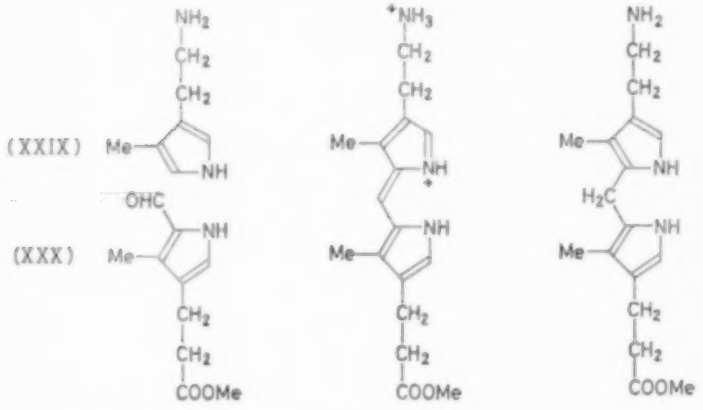
that condensation consequently might, *a priori*, lead to two differently substituted dipyrrylmethanes. However, we could assume with confidence that the condensation had taken the desired course, for steric and electronic reasons alike. Thus, the electron-withdrawing carbethoxy group deactivates the adjacent α-position for attack by an electron-deficient centre. By contrast, the electron-releasing methyl group activates the proximate position, and is at the same time the smaller group. Though relatively less susceptible to attack, for the reasons just outlined, the single free α-position in the dipyrrylmethane (XXIV) can fortunately be coaxed into reaction, and our next step was to condense that methane with β-carbomethoxypropionyl chloride through the agency of anhydrous zinc chloride. It will have been observed that the dicyanovinyl grouping in the resulting (XXV) has served the function of a concealed, relatively unreactive, acid-stable surrogate for the aldehyde group actually desired at C-2; the protecting group was now removed by the action of hot 33 per cent aqueous sodium hydroxide. After re-esterification of the carboxyl groups, both of which were freed under the very vigorous basic conditions of the cleavage reaction, the desired dicarbonyl compound (XXVII) was obtained. This substance seemed in itself a suitable right-hand component for our projected porphyrin synthesis, and the scheme was forthwith put to the test, with the readily available symmetrical dipyrrylmethane (XXVI) as the second, left-hand component. We were pleased to find even in initial experiments that when (XXVI) and (XXVII) were condensed in the presence of acidic reagents under mild conditions, reaction mixtures were obtained, from

VOL. 2 1961



(XXVI) (XXVII) (XXVIII)

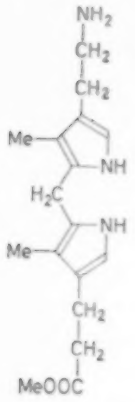
which, after oxidation with iodine, small amounts of porphyrin were formed, and more so to succeed, after assiduous variation of experimental conditions, in preparing the porphyrin (XXVIII) in the pure condition in a yield approaching 25 per cent. By any previous standard, this result approached the fabulous, but we knew that for our purpose it was still far from satisfactory. Let us consider the use, in such a reaction, of the actual left-hand component (XXXII) we had in mind. This substance was readily prepared by reduction of the dipyrromethene (XXXI), itself obtained by condensation of the aldehyde (XXX) with the aminoethyl pyrrole



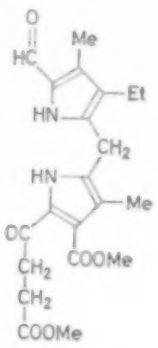
(XXIX) (XXX) (XXXI) (XXXII)

(XXIX). We may note again that two products might have been formed in this condensation, but in fact only the desired dipyrromethene (XXXI) was produced, no doubt largely in consequence of the relatively small bulk

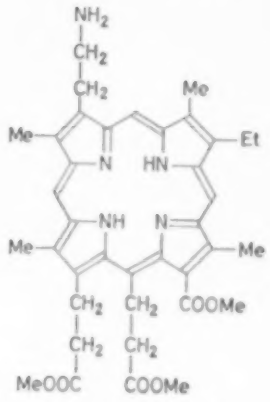
of the methyl group, but perhaps partly as a result of some electron withdrawal by the positively charged ethylammonium function. Now the new dipyrrylmethane (XXXIII) may be expected to, and in fact does, condense with the keto-aldehyde (XXXIV) to give, after the appropriate secondary treatment, the porphyrin (XXXV). But there is no reason to suppose that the components in this condensation will line up obligingly in that



(XXXIII)

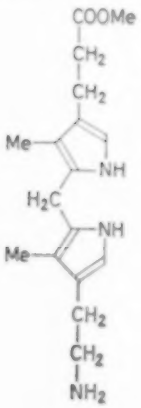


(XXXIV)

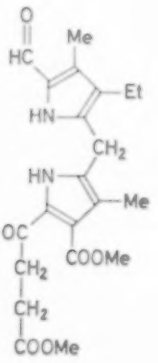


(XXXV)

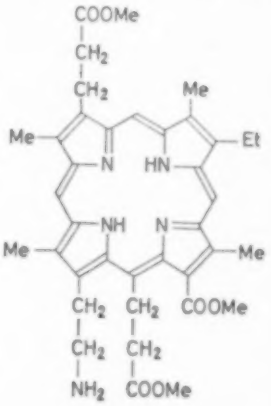
juxtaposition alone which leads to the desired product—nor do they. At the same time condensation takes place in the alternative sense (XXXVI + XXXVII), to produce a comparable amount of the isomeric porphyrin



(XXXVI)



(XXXVII)

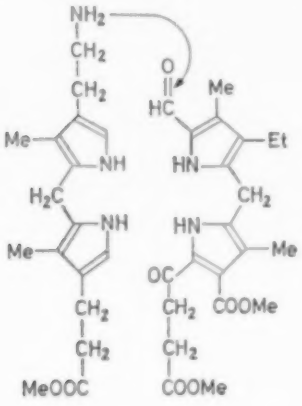


(XXXVIII)

(XXXVIII). Although the combined yield of the two porphyrins was not far below that which could be achieved in the simpler case, the amount of product useful for our purposes was severely curtailed. And how were we to ascertain which of the porphyrins obtained was that of the desired structure? Such inelegance, not to say impracticality, could not be

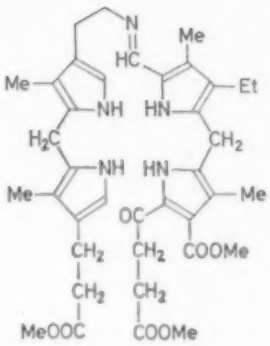
VOL. 2 1961

tolerated. Our plan for expunging it was simple in principle. We reasoned that a preliminary condensation between the aldehyde group of the right-hand component (XL) and the amino group of the left-hand component (XXXIX) might lead to a Schiff base of the structure (XLI), whose moieties



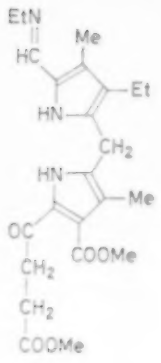
(XXXIX)

(XL)

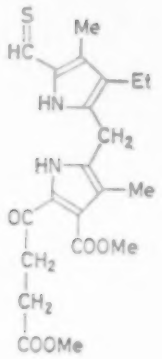


(XLI)

are held in a fixed relationship which would permit of no subsequent condensation other than that leading to a single product of the desired structure. The simplicity of this principle was by no means mirrored in a comparable ease of its reduction to practice. Indeed, its successful application required a long period of exacting and toilsome experimentation. First, it was found that pyrrole α-aldehydes, no doubt in consequence of interaction between the carbonyl group and the unshared electron pair on nitrogen, are relatively unreactive and do not condense with amines to give Schiff bases except under conditions of acid catalysis. We found that the aldehyde (XL) and other like substances could be brought into reaction with amines under acidic conditions as mild as those involving the use of a single molar proportion of triethylammonium acetate as catalyst in an inert solvent. But, dipyrrylmethanes such as (XXXIX), bearing only alkyl substituents, are diabolically sensitive compounds. They are torn to shreds and otherwise disastrously transmogrified in the presence of acidic reagents—even under the mildest conditions which we were able to define as necessary for Schiff-base formation. These circumstances conspired to yield a very clear-cut result in all of our early (and not so early) attempts to bring about our directed two-stage porphyrin synthesis—namely, not the slightest trace of porphyrin was obtained! Clearly, it was not possible to effect the desired preliminary reaction without rendering the left-hand moiety useless for the necessary subsequent changes. We did, however, in the course of these experiments, discover that the aldehyde (XL) was very smoothly converted, by ethylamine in the presence of acetic acid, into the simple Schiff base (XLII). Our next assault involved attempts to bring about the preliminary union of (XLII) with the left-hand component (XXXIX) by an amine-exchange reaction. These experiments showed some promise, and might

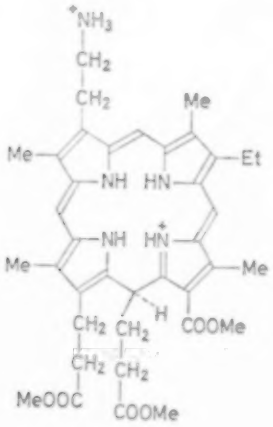


(XLII)



(XLIII)

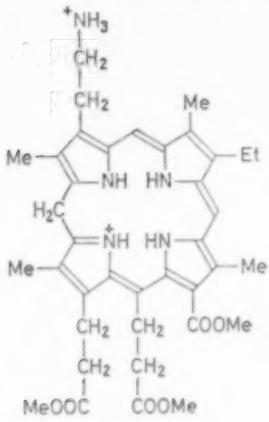
with considerable further expenditure of effort have been driven to a point at which they would provide a basis for a moderately satisfactory result, but they were rendered obsolete by the discovery that the *N*-ethylimino compound (XLII) could be converted smoothly, by hydrogen sulphide in benzene/methanol, to the thioaldehyde (XLIII). The latter was found to undergo extremely rapid condensation with primary amines in inert solvents, without necessity for catalysis. It was now no more than a matter of prolonged diligent experimentation to develop an entirely satisfactory method for the preparation of the extraordinarily sensitive Schiff base (XLI). The dipyrromethene (XXXI) is reduced in aqueous solution with a large excess of sodium borohydride, and the resulting dipyrrylmethane (XXXII) is extracted immediately into methylene chloride and treated at once with an equivalent amount of the thioaldehyde (XLIII). The methylene chloride solution is evaporated immediately, and the resulting Schiff base



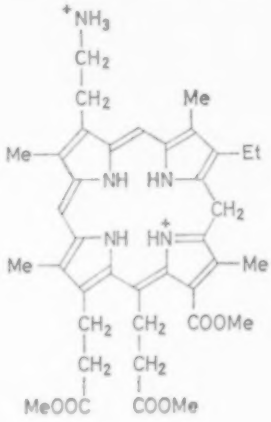
(XLIV)

VOL. 2 1961

(XLI) is introduced without delay into saturated methanolic hydrogen chloride at room temperature. The acid treatment of the Schiff base brings about a rapid and smooth conversion to the cation (XLIV), which we were able to isolate in the crystalline state as the dibromide. It is clear that the formation of the cation must proceed through several stages. Spectroscopic examination of the course of the reaction has provided evidence that a different, but similarly constituted, cation is first produced, and there is every reason to suppose that an initially formed bis(dipyrromethene) (see XVI) is immediately deprotonated to give either or both of the cations (XLV) and (XLVI). Tautomerization then leads to the more

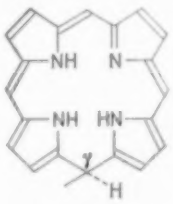


(XLV)



(XLVI)

stable isolable cation (XLIV); it is worthy of note that we see here, for the first time in our synthetic experiments, the operation of the steric compression factors which we discussed at some length earlier. The cation (XLIV) is a representative, in the salt form, of an entirely new class of substances. First found in the experiments just described, it will be encountered again in the sequel, and indeed we may mention further that we have prepared members of the class in several different ways. We feel certain that these substances will play a sufficiently important rôle in the future to justify their being given a class name, and we here designate compounds of the structure (XLVII) as *phlorins*. Phlorins give bright pure blue solutions in organic solvents, while similar solutions of the corresponding



(XLVII)

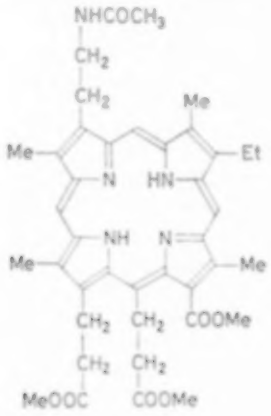
salts are green. Except in one respect, the phlorin salts are remarkably stable substances. They can be kept in solution in concentrated sulphuric acid for long periods of time without change, and survive treatment in acidic or neutral solvents at elevated temperatures for extended periods. The one sense in which they show instability lies in the great ease with which they are converted to porphyrins by oxidizing agents, such as oxygen, chloranil, or the halogens. It is interesting to speculate that the phlorin salts might be deprotonated, from carbon, to give an isophlorin of the structure (XLVIII); that fascinating array contains a continuous cyclic conjugated system, but it is one containing 20 π-electrons ($\neq 4n + 2$), and it might be considered reasonable for it to lose two electrons with ease, to

(XLVIII)

(XLIX)

give directly the porphyrin double salt (XLIX). Of course, it is also possible—and perhaps in acidic media more likely—that the oxidation involves direct attack of the oxidant upon the γ-hydrogen atom, or dehydrogenation of the true phlorin (XLVII) to an isoporphyrin (L). The latter species has not hitherto been encountered, or postulated, but we

(L)



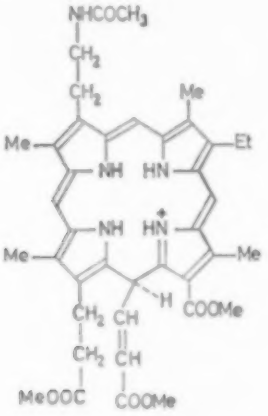
(LI)

hazard the opinion that it will be found to play a role in some base-catalysed reactions of the porphyrins.

To return now to the central topic of porphyrin synthesis, we found, in practice, that it was not desirable to isolate the intermediary cation (XLIV). Rather, the acid condensation reaction mixture was treated directly with excess iodine to effect oxidation; further, to facilitate isolation, the resulting

VOL. 2 1961

porphyrin was acetylated directly with acetic anhydride in pyridine. After this sequence, *the porphyrin (LI) could be isolated in the pure crystalline condition in an overall yield of* 50 *per cent from the components (XXXI) and (XLIII), introduced at the beginning of the series of five reactions.* Moreover, no other porphyrin was produced as a contaminant. After our description of the development of the method, it will come as no surprise that the experimental protocol for the sequence is exacting in the extreme; but to place the method in perspective, we may point out that our experience has demonstrated time and again that a skilful, patient and knowledgeable investigator can prepare the porphyrin (LI), almost a gramme at a time, in a precisely reproducible manner, and that during the course of our investigations, we have prepared upwards of 50 g of that substance. It is of some interest that the reactions are not carried out under conditions of high dilution, and that what might have been regarded as a formidable problem—the closure of a sixteen-membered ring—in fact presents no occasion for difficulty. No doubt the considerable elements of rigidity in the backbone of the open-chain precursor render the ring-formation reaction essentially comparable with that of a five- or six-membered ring from simpler progenitors.

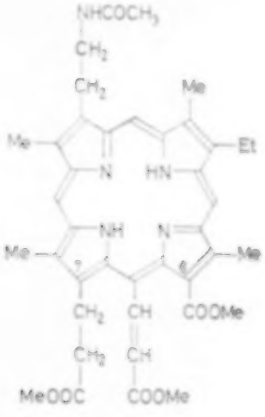


(LII)

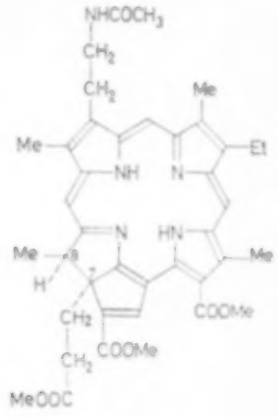
We turn now to the second major phase of our investigation. With the porphyrin synthesis well in hand, we had to come to grips with the problem of introducing the extra hydrogen atoms—those at positions 7 and 8 in chlorin e_6. It will be recalled that we considered in our planning the possibility that hydrogen atoms might be induced to wander to the desired positions from another site in a suitably constructed porphyrin. Were (LI) such a suitably constructed porphyrin, it was now time for the wandering to begin—and begin it did—though it stopped short of our desire! When the porphyrin (LI) was heated in acetic acid for a short time in the absence of air, a reaction mixture was obtained whose spectrum we recognized at once. It was that of a phlorin salt, and it soon became clear that the porphyrin had suffered ready acid-catalysed conversion to (LII). No doubt

we see here again the operation of the important steric factors to which we have repeatedly alluded; the formation of the phlorin salt is certainly assisted by the accompanying relief of strain, as the γ-carbon atom becomes tetrahedral, and the large attached chain is removed from the crowded molecular plane. Now it is easily possible to conceive of a plausible series of protonations and deprotonations which would provide a path for the conversion of phlorins into the isomeric chlorins. We have not as yet been able to realize this change. It is tempting to conclude that the great stability of the phlorin salts gives them a preferred position in any possible equilibrium with corresponding chlorins. But we regard that conclusion as premature. As far as we can say at present, it is quite as likely that at some point there is a high barrier between the two classes which we have not yet been able to surmount.

Like other phlorin salts, (LII) is readily oxidized by air, and, in consequence, when the porphyrin (LI) was warmed in acetic acid for a short while on the steam bath, without exclusion of air, it was converted quantitatively into the new porphyrin (LIII). When the latter, in its turn, was heated in acetic acid, for thirty hours at 110° under nitrogen, it was smoothly



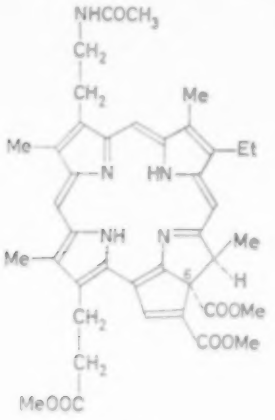
(LIII)



(LIV)

equilibrated with the purpurin (LIV) (purpurins are members of a sub-class of chlorins; the introduction of unsaturated substituents into the γ-position of the chlorin system frequently results in a change from the normal green to a purplish hue). *This remarkable reaction represents the first instance ever observed of reversible interconversion of a porphyrin and a chlorin.* Now we had come full circle! At the outset of our investigations we viewed the presence of a fused five-membered carbocyclic ring in the proposed formula for chlorophyll as a basis for suspicion of that formula, but were able to rationalize the difficulty on simple but cogent steric grounds. And here at this point in our work we encountered the smooth closure of a not dissimilar ring, in a process which must certainly be driven forward by just the same factors of steric compression which we discerned so much earlier. For it is not

difficult to conceive of a path which permits the interconversion of our porphyrin and our purpurin, but it may be doubted that the purpurin would predominate as much as it does in the equilibrium between the two substances were its ring not forced shut by the crowding in the highly substituted porphyrin. In fact, the equilibrium constant is 5:3 in favour of the purpurin, and since the equilibrium is cleanly established, it is possible, through recycling, to effect the preparation of the purpurin (LIV) from its precursor in almost 70 per cent yield. A second point relevant to this equilibrium is of great moment. Why does the reaction proceed in the sense indicated, rather than to give the alternative product (LV), by a similar cyclization involving formation of a new bond to C–6? It is of

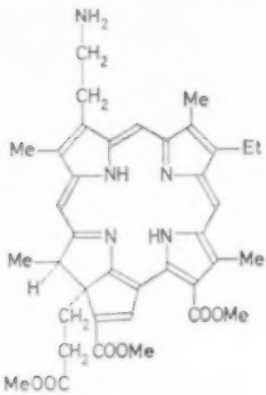


(LV)

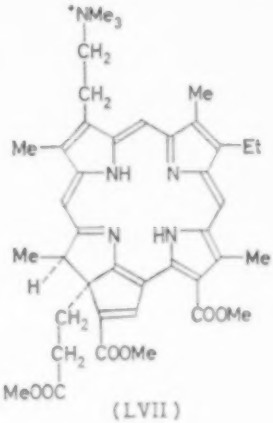
much interest that (LV) is, in fact, a very minor participant in the equilibrium system; it too has been isolated and characterized, and its properties leave no doubt about its relationship to (LIV). It will be noted that, in the formation of (LV), the carbomethoxy group at C–6 is removed from conjugation, while no such adverse factor is involved in the formation of the major product (LIV). Further, it may be suspected that the difficult steric situation in the porphyrin (LIII) is more effectively relieved by the changes leading to (LIV) than by those which give (LV). Finally, we should take note of the fact that the stereochemistry of our purpurin may be adopted with confidence as written, since in an equilibrium process the more stable of two possible stereoisomers will be formed; there can be no doubt that (LIV) represents a more stable arrangement than that in an isomeric substance whose methyl and propionic ester groups, at C–8 and C–7 respectively, are on the same side of the molecular plane.

In the purpurin (LIV), our task of placing hydrogen atoms at C–7 and C–8 was half done, in that one of the two needed had been placed at C–8. Further, we should emphasize that the method of its placement is a most satisfying one in that it is structurally significant—that is, the reaction involved is one which can place the atom in question only at the desired position and no other. It was now necessary to consider the removal, and

replacement by another hydrogen atom, of the platform from which the first was delivered. But first a simple but important change elsewhere in the molecule should be described. The acetylamino-group of the purpurin (LIV) was readily hydrolysed, by hot 1N methanolic hydrogen chloride, and when the resulting amino-compound (LVI) was treated with excess of methyl sulphate and methanolic sodium hydroxide, the vinyl purpurin (LVIII) was produced directly in high yield. Clearly, the intermediary trimethylammonium compound (LVII) not surprisingly, suffers very ready

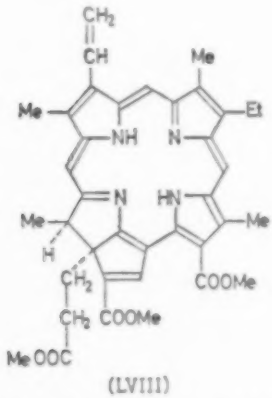


(LVI)

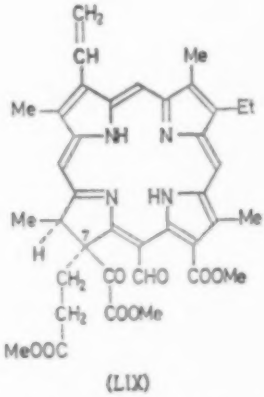


(LVII)

Hofmann elimination. Now the new purpurin (LVIII) was found to be susceptible to a most extraordinary and useful change. When it was illuminated strongly with visible light, in the presence of air, it was rapidly and smoothly transformed into the keto-aldehyde (LIX). It should be



(LVIII)

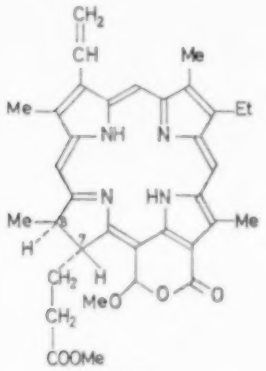


(LIX)

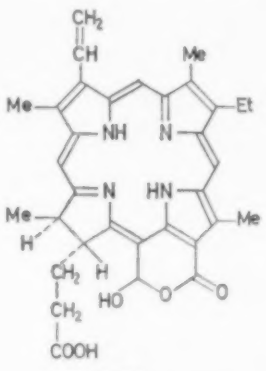
noted that the reaction is highly selective, in that neither the chlorin ring system nor the attached vinyl group is attacked in the slightest degree. It is quite possible that the strain within the five-membered ring of (LVIII) is a factor in bringing about this high selectivity, but we suspect that special

electronic factors beyond our present powers of delineation may be involved at least in equal measure. In any event, it may be regarded as singularly appropriate that a photochemical reaction should play a prominent role in the synthesis of chlorophyll.

The methoxalyl group at C–7 in the purpurin (LIX) is so placed that it may be expected to suffer ready cleavage from the nucleus to which it is attached by basic reagents. And indeed, when (LIX) was treated with dilute methanolic potash, the anticipated change did occur. At the same time, independently, the base attacked the aldehyde group in an entirely predictable manner, and the product of the reaction was the methoxy-lactone (LX). The latter is the racemic form of a known substance,



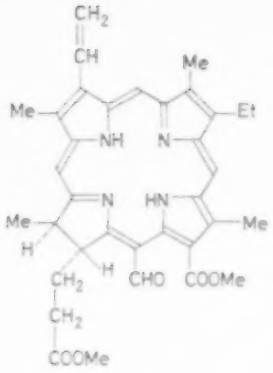
(LX)



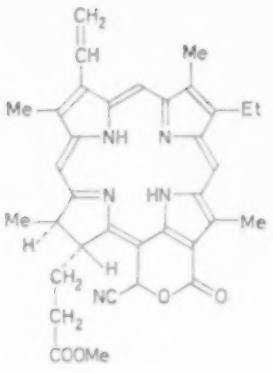
(LXI)

isopurpurin 5 methyl ester, which was prepared[4] many years ago—though formulated in a different, incorrect, manner—in Fischer's laboratory, by degradation of chlorophyll. Consequently, at this point we were able, for the first time, to establish a connection with natural materials; the quantitative infra-red spectra in solution, and the visible spectra of the synthetic racemic ester and the corresponding optically active material of natural provenance were identical in every respect. It is of importance to note that the method of synthesis of isopurpurin 5 methyl ester confirms the *trans* disposition of the hydrogen atoms at C–7 and C–8. For, in addition to the normal preference for retention of configuration in electrophilic displacements at carbon, there is in the case at hand the added factor that inversion at C–7 would involve passage of the propionic ester chain at C–7 through a molecular plane much crowded by the substituents in the γ-position.

When the synthetic isopurpurin 5 methyl ester was hydrolysed with very dilute sodium hydroxide in dioxane/water, it was transformed into racemic chlorin 5 (LXI), which was then converted into a mixture of the corresponding diastereomeric quinine salts. The resolution of the mixture was not especially easy, since both salts crystallized, but, when the proper conditions had been defined, it proceeded with high efficiency. One of the salts so obtained was identical in every respect with a similar substance prepared from natural materials, as was the chlorin 5 regenerated from it[5].



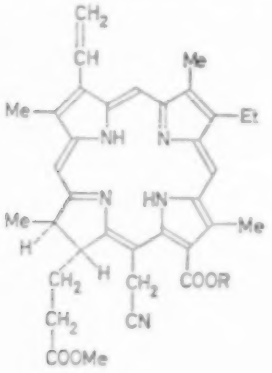
(LXII)



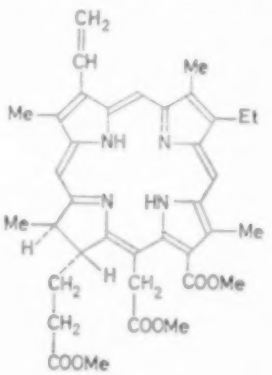
(LXIII)

Further, when the resolved chlorin 5 was treated with diazomethane, it was converted to totally synthetic optically active purpurin 5 dimethyl ester (**LXII**), which was identical in all details with a sample of natural origin[6].

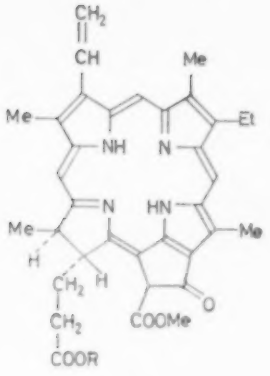
When purpurin 5 dimethyl ester (**LXII**) was treated briefly with hydrogen cyanide in dichloromethane in the presence of triethylamine, it was converted in very high yield into the cyanolactone (**LXIII**)[7]. The lactone, treated for a very short time with zinc and acetic acid, was reduced to the acid (**LXIV**, R = H), which, with diazomethane, gave the ester (**LXIV**, R = Me). Treatment of the latter with methanolic hydrogen chloride at room temperature resulted in methanolysis of the nitrile group, and chlorin e_6 trimethyl ester (**LXV** ≡ **VIII**), identical in every detail with an authentic sample, was obtained. Our objective had now been reached, and the total synthesis of chlorophyll *a* was complete, since, as we have mentioned earlier, the short path from chlorin e_6 back to the chlorophyll *a*, from which the key intermediate is readily obtainable, had been laid down in the early work of Willstätter and Hans Fischer[1]. Thus, Dieckmann cyclization of the ester under the influence of sodium methoxide gives methyl phaeophorbide *a* (**LXVI**, R = Me), one of whose methyl ester groups can be



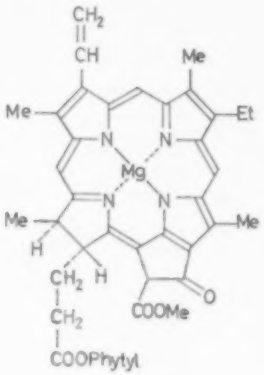
(LXIV)



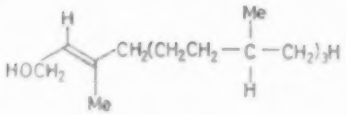
(LXV)



(LXVI)



(LXVII)



(LXVIII)

replaced by a phytyl group, either by chemical or enzymatic means. Then, the magnesium atom may be introduced into the resulting phaeophytin *a* (LXVI, R = Phytyl), through the agency of basic magnesium halides, to give chlorophyll *a* itself (LXVII ≡ I). We should not neglect to acknowledge at this point the contribution of Burrell, Jackman, and Weedon, who only last year established the stereochemistry of, and synthesized, optically active phytol[8] (LXVIII), which, though its rôle in the chemistry of chlorophyll is minor, is none the less an integral part of the complete molecule.

Now that the synthetic phase of our interest in chlorophyll has been brought to a successful conclusion, it is perhaps worth while to look back briefly in a very general way over the development of the investigation. As all projects of such magnitude must be, this one was planned in a fairly elaborate way at the outset. The measure in which our initial plans were realized is very gratifying, but it is at least equally so that major elements of discovery, and increase in understanding through observation and experiment, were involved in our progress. We learned and established much about this important class of compounds which could not have been known, or at best could only have been dimly foreshadowed, before our work was carried out. This fascinating aspect of work in chlorophyll chemistry has by no means been exhausted—indeed, we feel that our studies have opened up many more avenues than they have traversed, and we do not hesitate to hazard the opinion that the area is one from which much increase in chemical knowledge and understanding is to be had in the future.

It remains to thank with all the warmth at my command those who fought and enjoyed the battle with me. During the first year (1956–57), I had the good fortune to be associated with Drs John M. Beaton, Gerhard

Closs, Albert Langemann, and Zdenek Valenta. These men did much exploratory work, established the validity of our general approach to porphyrin synthesis, and made the observations which provided an important clue to the problem of passing the barrier between the porphyrins and the chlorins. Their places were taken, during 1957–58, by Drs William A. Ayer, John Hannah, and Fred P. Hauck. This second group did much to develop and improve the methods of synthesis of our dipyrrylmethane intermediates, performed Herculean preparative tasks, and brought much further understanding to our studies of chlorin formation. They, in their turn, were replaced (in 1958–59) by Drs Raymond Bonnett, Hans Dutler, Shô Itô, Jürgen Sauer, and Heinrich Volz, whose victory it was to bring our orientationally directed porphyrin synthesis into being. Of this group, Dr Dutler remained for half of the succeeding year, and was joined by Drs Paul Buchschacher, Friedrich Bickelhaupt, Eugene Le Goff, Willy Leimgruber, and Walter Lwowski, who brought the work to its successful conclusion. It has been a great privilege to share with these men the pleasures and vicissitudes of a long and fascinating journey. Finally, all of us wish to express our warm appreciation to the National Institutes of Health, the National Science Foundation, and Research Corporation for generous support, to Chas. Pfizer and Co., Inc., for support and invaluable assistance in the preparation of primary intermediates in quantity, to Professor Dr Arthur Stoll and Sandoz A.G. for a handsome gift of methyl phaeophorbide *a*, and to Drs Stephan Sallay and Wolfgang H. F. Sasse for their co-operation in certain phases of our work.

VOL. 2 1961

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CHEMISTRY OF THE ACTINOMYCINS

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The actinomycins are yellow-red crystalline antibiotics that are produced by various species of *Streptomyces*. *Streptomyces* is a genus of soil microbes that, on the basis of its morphology, has a position between the fungi and the bacteria.

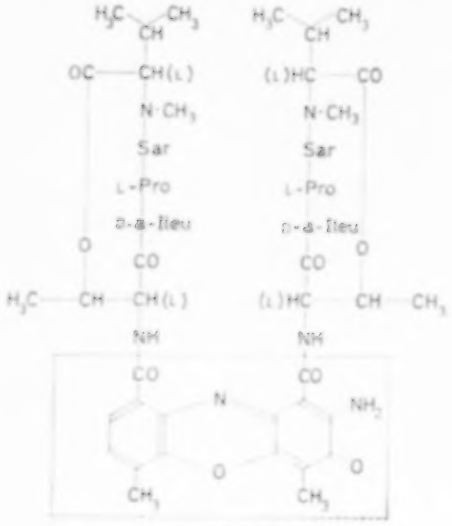
The actinomycins are highly toxic and cannot, therefore, be used in the treatment of infectious diseases. They are, however, of interest because in small, non-toxic dosages they have an anti-cancer effect in laboratory animals, and in man a favourable effect on Hodgkin's disease, a cancer-like disease of the lymphatic system. Moreover, it has been observed that actinomycins are able to stop the development of various human tumours, and to increase the effect of radiotherapy in the treatment of some forms of tumours[1, 2].

During the last few years we have been investigating the structure of the actinomycins. In the course of these studies, we have been able to clarify the constitution of some of them, and to find a method for their synthesis. A brief account of this work[3] will be given here.

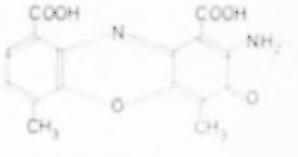
Strains of *Streptomyces* able to synthesize actinomycins usually produce several actinomycins simultaneously. These mixtures of actinomycins form mixed crystals, and cannot be separated by fractional crystallization. In the early investigations, these mixtures were believed to be homogeneous substances. Methods for the separation of such actinomycin mixtures by counter-current distribution or partition chromatography were first developed in our Institute[4]. By means of these methods, it was possible to separate small quantities of actinomycins and to identify them by their R_F values. Moreover, it was then possible to obtain homogeneous actinomycins in larger quantities, so that thereafter all experiments designed to clarify the structure of the actinomycins were on a sure basis. In the course of our investigations, we have isolated from different strains of *Streptomyces* nine crystalline actinomycins, and the total number has been raised to twenty-four by other workers.

The first chemical investigations carried out with mixtures of actinomycins by Todd, Johnson and co-workers[5], as well as by the author and co-workers[6], showed that the molecule of the actinomycins consists of a polypeptide moiety and a part responsible for the yellow-red colour of the compounds. Thus the actinomycins are representatives of a new class of natural products which can be named " chromopeptides ".

When homogeneous actinomycins were at our disposal, we continued our work on their structure and decided to concentrate initially on one of the actinomycins, namely actinomycin C_3. By hydrolysis of actinomycin C_3 with dilute and with concentrated hydrochloric acid, or with dilute sodium hydroxide, we obtained a number of degradation products, the structure of which enabled us to propose[7] for actinomycin C_3 the formula (I).



Actinomycin C_3 (I)



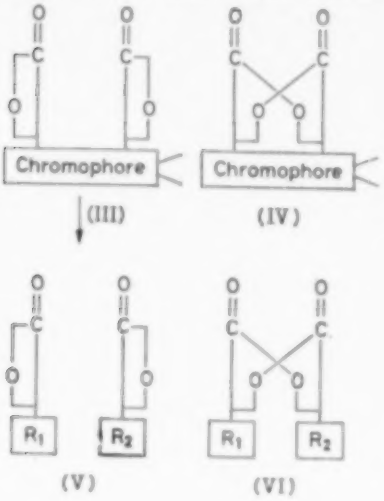
Actinocin (II)

The dotted line in formula (I) circumscribes the chromophore of actinomycin C_3 responsible for its yellow-red colour. This chromophore is the residue of the amino-phenoxazone-dicarboxylic acid (II) which we have named " actinocin ".

In the molecule of actinomycin C_3 (I), this actinocin (II) is linked by amide bonds derived from its two carboxyl groups to two identical peptide lactone groups. It is remarkable that these peptide groups contain four methylamino-acids, namely two molecules of sarcosine and two molecules of *N*-methyl-valine. It is also remarkable that the two molecules of allo-isoleucine between the threonine and the proline have the " unnatural " D-configuration.

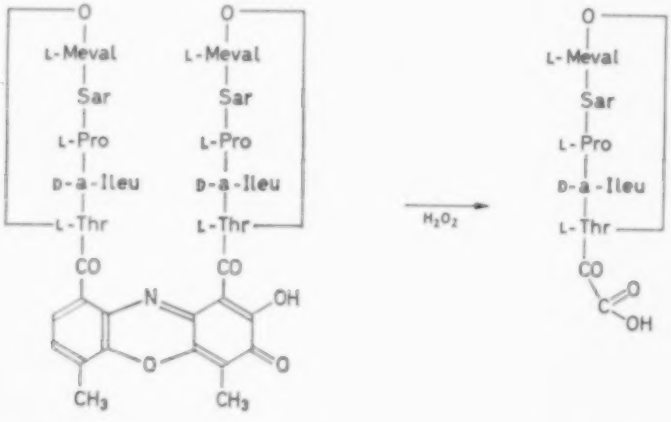
Until recently, it could not be decided with certainty whether the carboxyl groups of the two *N*-methyl-valine residues at the end of each of the peptide chains were esterified with the threonine of the same peptide chain, as in formula (I), or with the hydroxyl group of the threonine of the other peptide chain. This alternative is demonstrated by the two simplified formulae (III) and (IV). To decide between these two formulae, we tried to split the chromophore into two parts without opening the lactone rings. If structure (III) were correct, such a degradation would give two fission products (V) each containing one of the peptide lactone rings of the original actinomycins. The groupings R_1 and R_2 linked to the peptide lactone groups represent fragments of the chromophore. The isolation of only one of these fission products would suffice to establish the correctness of the structure (III). On the other hand, if the actinomycin were correctly represented by (IV), the envisaged fission of the chromophore would give a monocyclic degradation product (VI), in which the ring would contain two peptide units and two lactone groups.

VOL. 2 1961

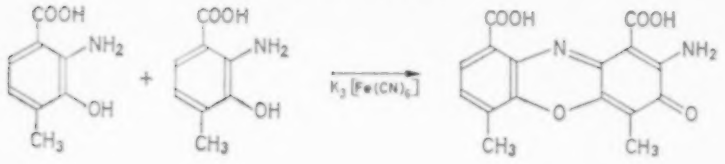


A fission of the chromophore which did not harm the peptide groups was achieved by oxidation of desamino-actinomycin C_3 (VII), a derivative which can be obtained in nearly quantitative yield by mild hydrolysis of actinomycin C_3 (I) with dilute hydrochloric acid. Treatment of desamino-actinomycin C_3 (VII) with hydrogen peroxide in acetic acid yielded a colourless crystalline degradation product which was shown to have the structure (VIII). In other words, the degradation product contains one intact peptide lactone group of the actinomycin C_3, thus proving that actinomycin C_3 has two peptide lactone groups[8], as shown in formula (VII).

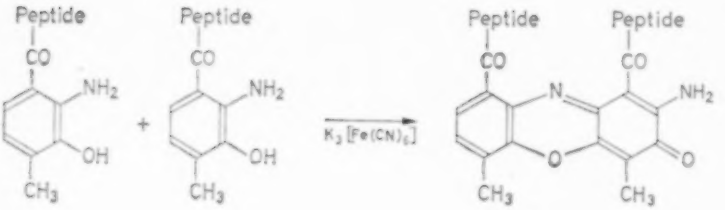
The structure of the actinomycin C_3, in particular the fact that it contains two identical peptide groups, raises the question of how the actinomycins are synthesized in the cell.



Desamino-actinomycin C_3 (VII) (VIII)



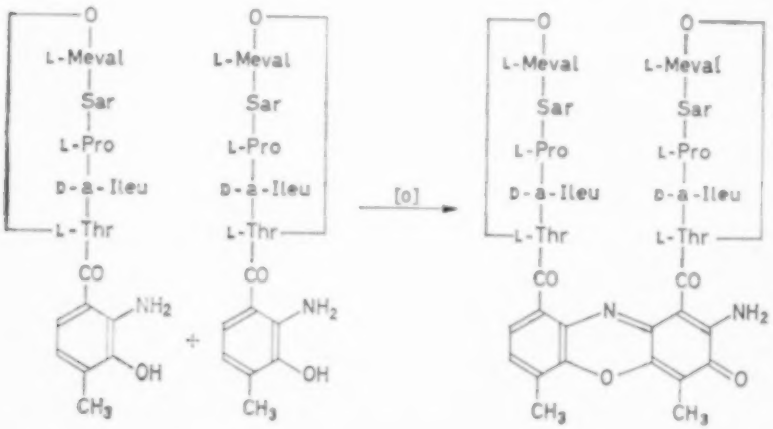
(IX) (IX) Actinocin (X)



(XI) (XI) Actinocinyl-peptide (XII)

VOL. 2 1961

We arrived at a hypothesis for this biosynthesis from the results of experiments on the synthesis of the chromophore of actinomycin C_3. This chromophore can be produced[9] easily by oxidative condensation of two molecules of 3-hydroxy-4-methylanthranilic acid (IX). A similar condensation is possible when the acid (IX) is linked *via* its carboxyl group to the amino group of an amino-acid, dipeptide, tripeptide, or tetrapeptide, as is indicated by the general formulae (XI) and (XII). In this way, we were able to synthesize a number of actinocinyl-peptides of the general formula (XII) from precursors similar to (XI). The observation that these condensations can be carried out in water at pH 7·8 with air as an oxidant, led us to the assumption[7] that the actinomycins are synthesized *in vivo* in a

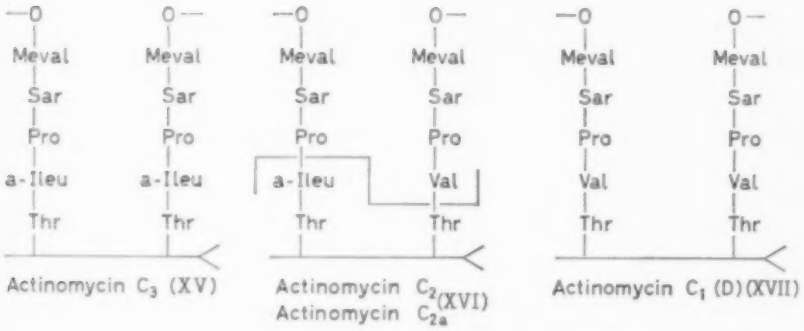


(XIII) Precursor (XIII) Actinomycin C_3 (XIV)

similar way. Actinomycin C_3 would then be built up by the oxidative condensation of two molecules of a precursor (XIII). On this hypothesis, from two precursors of type (XIII) differing only in the structure of their peptide groups, the cell should be able to synthesize four different actinomycins: two with identical and two with different peptide groups. How far this prediction is in accordance with the experimental findings will be discussed later.

After the structure of actinomycin C_3 had been determined, we turned our attention to the question of how the other actinomycins differ from actinomycin C_3. As has already been mentioned, strains of *Streptomyces* able to synthesize actinomycins usually produce a mixture of different actinomycins. An investigation of the actinomycin mixtures of twenty-one strains showed us that these strains can be classified into three groups according to the composition of their actinomycin mixtures. One of these groups produces an actinomycin mixture, designated with the letter C, that contains the actinomycins C_3 and C_2 as main components and actinomycin C_1 in smaller amounts.

By means of the same degradation methods as those[10] employed for the investigation of actinomycin C_3, we were also able to establish the structures of actinomycins C_1 and C_2[11]. They have the same chromophore as actinomycin C_3, and differ from it only slightly in the structure of their peptide



(XVIII) (XIX)

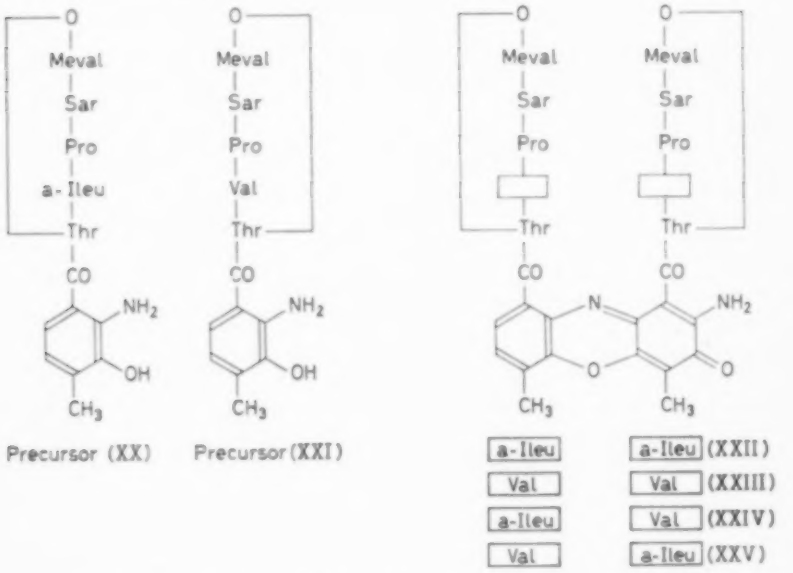
groups. For discussion of these differences it will be convenient to simplify the structural formulae in the manner which is illustrated in the case of actinomycin C_3 (I) by formula (XV). The chromophore is symbolized by a horizontal line, and the amino and carbonyl group associated with it by two short diagonal dashes. The roman capitals indicating the configuration of the amino- and methylamino-acids are omitted, and the lactone bond between the *N*-methyl-valine and the threonine is represented by a short dash.

Actinomycin C_1 (XVII) differs from actinomycin C_3 (XV) only in that it contains two molecules of valine (XVIII) instead of two molecules of allo-isoleucine (XIX). In this connection it should be noted that, on the basis of degradation experiments, Johnson and Bullock[12] concluded that actinomycin D (described for the first time in 1954 by Waksman and Vining[13]) also has the constitution (XVII). This proves unequivocally that actinomycin D is identical with our actinomycin C_1, which was first described in 1952. Moreover, one of the three groups of actinomycin-producing strains mentioned above is characterized by the fact that it produces an actinomycin mixture containing predominantly actinomycin C_1.

Actinomycin C_2 (XVI) holds an intermediate position between actinomycin C_1 and C_3. One of its peptide groups has the same structure as the peptide groups of actinomycin C_3 (XV) and the other as the peptide groups of actinomycin C_1 (XVII).

At first we could not eliminate the possibility that actinomycin C_2 (XVI) is a mixture of two isomers, one having the valine and allo-isoleucine in the positions shown in formula (XVI), and the other having the positions of these units interchanged as indicated by the serpentine line of formula (XVI). Recently, however, we have been able to show by degradation experiments (not discussed here) that actinomycin C_2 is homogeneous and not a mixture of two isomers.

VOL. 2 1961



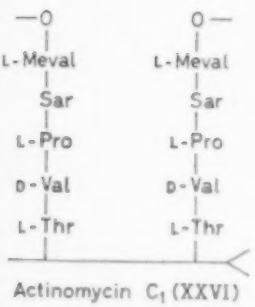
According to our hypothesis of the biosynthesis of the actinomycins, those strains of *Streptomyces* which produce actinomycins C_1, C_2 and C_3 simultaneously, would need two precursors for this synthesis. One of them (XXI) has D-valine, and the other (XX) has D-allo-isoleucine, in the peptide group. Oxidative condensation of two molecules of the precursor (XXI) would give actinomycin C_1 (XXIII). Analogous condensation of two molecules

of the precursor (XX) would give actinomycin C_3 (XXII). On the other hand, if one molecule of the precursor (XX) is condensed with one molecule of the precursor (XXI), the formation of two isomers is to be expected, one that has the valine in the left-hand peptide group and the allo-isoleucine in the right-hand peptide group as in the formula (XXV), and the other with the positions of these two acids reversed as in formula (XXIV). One* of these two isomers is actinomycin C_2.

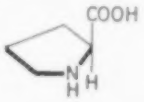
An indication of the existence of the second isomer is given by an actinomycin which we have isolated from *Streptomyces* cultures producing actinomycins C_1, C_2 and C_3. This new compound, which we have named[14] actinomycin C_{2a}, and which differs only slightly in its R_F value from actinomycin C_2, contains the same amino and methylamino acids as actinomycin C_2. Up to now we have obtained only small quantities of this new actinomycin, so that we have not as yet been able to determine the exact structure of its peptide groups. But, in all probability, actinomycin C_{2a} is the isomer of actinomycin C_2 whose existence is to be expected on the basis of our hypothesis.

As already mentioned, all strains of *Streptomyces* investigated in our Institute can be classified into three groups according to the composition of their actinomycin complexes. It will be recalled that one of these groups produces a mixture of the actinomycins C_1, C_2 and C_3, and another group a mixture containing mainly actinomycin C_1. The third group synthesizes an actinomycin mixture that we have designated with the letter X[4, 15]. This mixture consists of a main component, named actinomycin X_2, and a number of other actinomycins, among them actinomycin C_1. We have shown that all components of the actinomycin mixture X have the same chromophore as actinomycins C_1, C_2 and C_3. Consequently, they differ from each other, and from the C actinomycins, only in the structure of their peptide units.

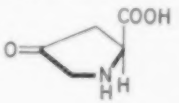
Actinomycin X_2, the main component of the actinomycin complex X, is characterized by the fact that it contains one molecule of L-γ-oxo-proline[16] (XXVIII). Two other components contain L-hydroxy-proline (XXX) or L-allo-hydroxy-proline (XXIX). The γ-oxo-proline (XXVIII) is a derivative of proline that was unknown before 1956. It was first synthesized by



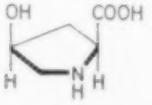
Actinomycin C_1 (XXVI)



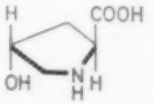
L-Proline (XXVII)



L-γ-Oxo-proline (XXVIII)



L-allo-Hydroxy-proline (XXIX)



L-Hydroxy-proline (XXX)

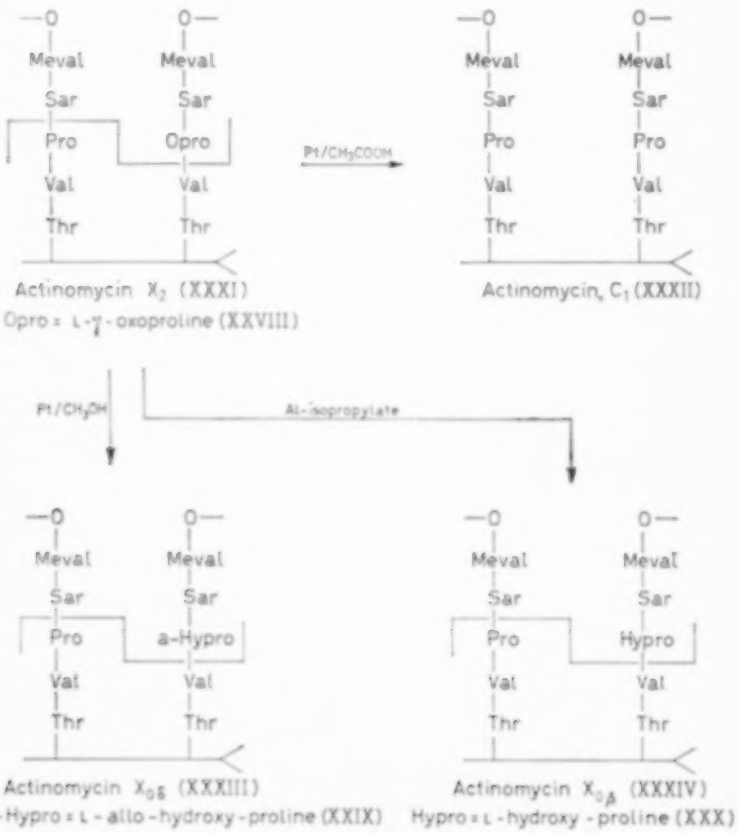
*This has now been shown to be (XXV)[33].

Kuhn and Osswald[17]. These authors showed that γ-oxo-proline—in the form of carbethoxy-oxo-proline-ethylester—is reduced to proline by catalytic hydrogenation in acetic acid, and to allo-hydroxy-proline by catalytic hydrogenation in methanol. If, on the other hand, the reduction is carried out with aluminium iso-propylate, a mixture of the hydroxy-proline and allo-hydroxy-proline derivatives is formed.

We have found that actinomycin X_2 differs from actinomycin C_1 (XXVI) in that it contains one molecule of L-γ-oxo-proline (XXVIII) in place of one molecule of L-proline (XXVII). Actinomycin $X_{0\beta}$[18], another component of the actinomycin complex X, differs from actinomycin C_1 in that it contains one molecule of L-hydroxy-proline (XXX) in place of one molecule of proline (XXVII).

Finally, actinomycin $X_{0\delta}$[19], which can also be a component of the actinomycin complex X[20], differs from actinomycin $X_{0\beta}$ only in that it contains one molecule of L-allo-hydroxy-proline (XXIX) in place of one molecule of L-hydroxy-proline (XXX).

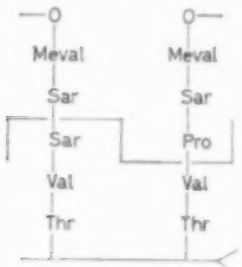
The close structural relationship of the actinomycins X_2, $X_{0\beta}$, $X_{0\delta}$ and C_1 was disclosed by reduction studies. Catalytic hydrogenation in acetic



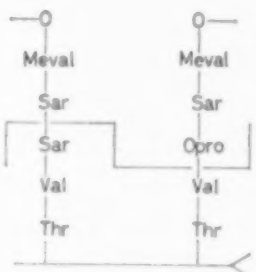
acid over a platinum catalyst reduces actinomycin X_2 to actinomycin C_1 (XXXII), thus proving that actinomycin X_2 differs from actinomycin C_1 only in that it contains one molecule of L-γ-oxo-proline in place of one molecule of L-proline[20]. Actinomycin X_2 can thus be given the formula (XXXI).

Reduction by means of aluminium iso-propylate converted the actinomycin X_2 (XXXI) into actinomycin $X_{0\beta}$, whereas catalytic hydrogenation of actinomycin X_2 in methanol gave actinomycin $X_{0\delta}$. On the basis of these results the formulae (XXXIV) and (XXXIII) can be attributed to the actinomycins $X_{0\beta}$ and $X_{0\delta}$ respectively[20]. The serpentine line in these formulae as well as in (XXXI) indicates that it is still uncertain whether the proline is a part of the left-hand or of the right-hand peptide group.

According to the formulae (XXXIII) and (XXXIV), actinomycin $X_{0\beta}$ is a stereoisomer of actinomycin $X_{0\delta}$, differing from it only in the configuration of the hydroxyl-substituted carbon atom of the L-hydroxy-proline. This slight distinction is sufficient to cause a marked difference in the solubility of the two stereoisomers, and also in their antibiotic activity. For instance, actinomycin $X_{0\delta}$ is about three times as soluble as actinomycin $X_{0\beta}$ in methanol containing 5 per cent water, and it is about ten times as active against *Bacillus subtilis* as actinomycin $X_{0\beta}$.



Actinomycin $X_{0\gamma}$ (XXXV)

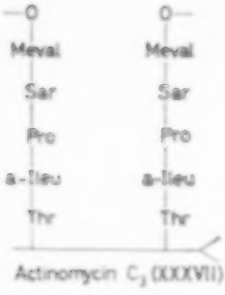


Actinomycin X_{1a} (XXXVI)

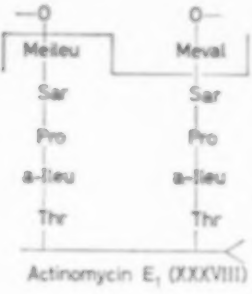
We have found a new variation of the peptide moiety in two other components of the actinomycin complex X; we have named these[20] actinomycin $X_{0\gamma}$ and actinomycin X_{1a}. A comparison of their formulae ((XXXV), (XXXVI)) with that of actinomycin C_1 (XXXII) shows that actinomycin $X_{0\gamma}$ (XXXV) can be considered as a derivative of actinomycin C_1, one molecule of sarcosine being substituted for one molecule of proline. Likewise, actinomycin X_{1a} (XXXVI) may be regarded as being a derivative of actinomycin C_1, one molecule of sarcosine and one molecule of γ-oxo-proline being substituted for the two molecules of proline. The serpentine line in the formulae again indicates that the positions of the proline and sarcosine, or of the oxo-proline and sarcosine, have not been ascertained and could in fact be the reverse of that shown. At this point it must be mentioned that Johnson and Mauger[21] have investigated an actinomycin, designated with the number III, and shown it to have the same amino- and methylamino-acids as actinomycin $X_{0\gamma}$. Whether our actinomycin $X_{0\gamma}$ is identical with actinomycin III, or whether it is an isomer, remains to be established.

After the actinomycins had been shown to be chromopeptides, the question arose whether the actinomycin-producing organisms could be stimulated to incorporate into the actinomycin molecule amino- or methylamino-acids that had been added to the culture broth. That this is indeed the case was demonstrated for the first time by Schmidt-Kastner[22]. After addition of either sarcosine or DL-isoleucine to the culture broth of strains producing actinomycin C_1, C_2 and C_3, he was able to isolate from the cultures a number of new actinomycins in addition to those normally formed.

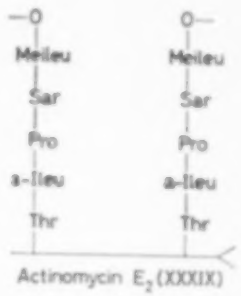
In co-operation with Schmidt-Kastner, we have made quantitative determinations of the amino- and methylamino-acids of the new actinomycins. Moreover, we have identified in their peptide groups those methylamino-acids that are esterified with the threonine residues. We cannot yet give an exact proof of any sequence of the amino-acids of the new



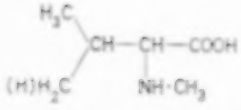
Actinomycin C_3 (XXXVII)



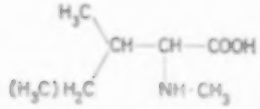
Actinomycin E_1 (XXXVIII)



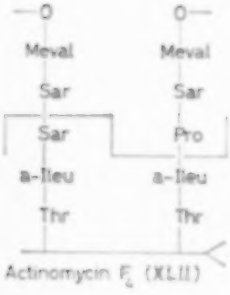
Actinomycin E_2 (XXXIX)



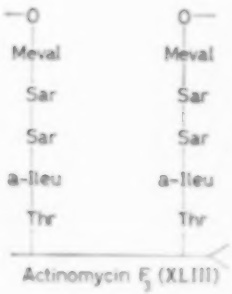
N-Methyl-valine (Meval) (XL)



N-Methyl-isoleucine (Meileu) (XLI)



Actinomycin F_2 (XLII)



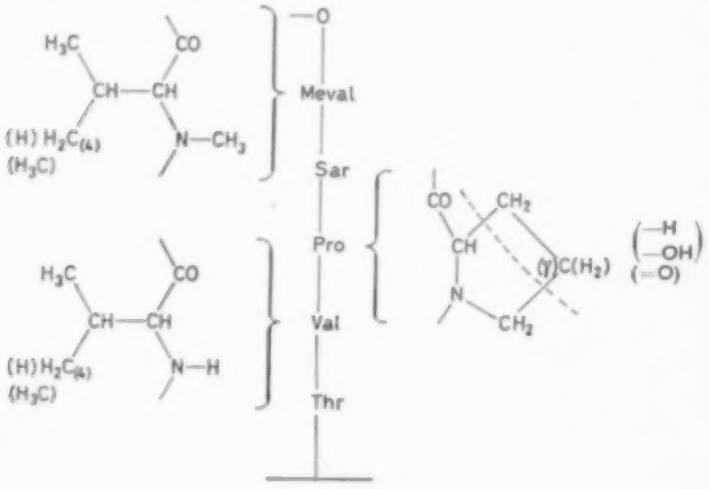
Actinomycin F_3 (XLIII)

actinomycins produced by the so-called " directed biosynthesis ". If, however, it is assumed that the " directed biosynthesis " is controlled by a tendency to make the structural differences between the actinomycins of the " directed biosynthesis " and the " normal" actinomycins as slight as possible, we arrive at the formulae (XXXVIII)–(XLIII).

The actinomycins E_1 (XXXVIII) and E_2 (XXXIX) are formed when DL-isoleucine is added to the culture broth of strains normally producing mixtures of the actinomycins C_1, C_2 and C_3. As the formulae show, the addition of DL-isoleucine induces the strain to vary the molecule of actinomycin C_3 by replacing one or both molecules of *N*-methyl-valine (XL) by *N*-methyl-isoleucine (XLI).

A second group of new actinomycins, named actinomycins F_1, F_2, F_3, F_4 and F_5, was formed when sarcosine was added to the culture broth of strains " normally " producing the actinomycins C_1, C_2 and C_3. The formulae of actinomycin F_3 and F_4 are given by (XLIII) and (XLII) respectively. A comparison with the formula of actinomycin C_3 shows that the presence of sarcosine induces the cell to incorporate into the peptide groups one or two molecules of sarcosine instead of proline. In the same way the peptide groups of the actinomycin C_1 and C_2 can be varied by the cell.

Summarizing the above results on the structural differences of the peptide moiety of the actinomycins, one arrives at the following conclusions. In all actinomycins that we have investigated, the two carboxyl groups of the chromophore, which in all actinomycins has the same structure, are bonded to the amino group of two molecules of threonine. Variations in the structure of the peptide groups have been found in three constituents of these peptide groups, as is shown by (XLIV). The latter is the simplified formula of one of the two peptide groups of the actinomycin C_1. These groups may be regarded as the " basic structure " of an actinomycin peptide group.



(XLIV)

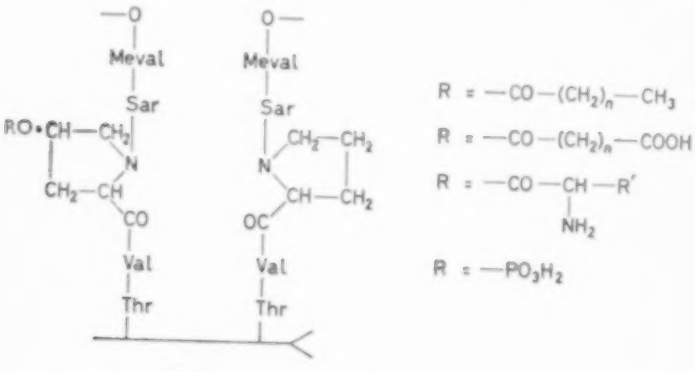
This " basic structure " can be varied at the valine and at the *N*-methyl-valine positions by substitution of a methyl group for a hydrogen atom at $C_{(\beta)}$. By this substitution the valine is converted into allo-isoleucine and the *N*-methyl-valine to *N*-methyl-isoleucine; variations of this type are possible in either or both of the peptide groups.

The proline residue can be varied firstly by the substitution of a hydroxyl group for one of the two hydrogen atoms at the γ-carbon atom, and secondly by the substitution of a carbonyl oxygen atom for the two hydrogen atoms at the γ-carbon atom of the proline. Finally, one or two molecules of sarcosine can be substituted for molecules of proline; in other words, the $-CH_2-CH_2-$ group of the proline—see dashed line in formula (XLIV)—can be replaced by two hydrogen atoms.

Obviously there exist still other variations of the peptide groups. Recently Keller-Schierlein[23] and co-workers have isolated five actinomycins, named actinomycin Z_1, Z_2, Z_3, Z_4 and Z_5, that all contain *N*-methyl-alanine. Some actinomycins similar to these have been isolated in our laboratory. Moreover, Katz and Goss[24] have described actinomycins containing pipecolic acid. These actinomycins were produced by the addition of pipecolic acid to the culture broth.

In view of the fact that, up to now, twenty-four different actinomycins have been isolated from *Streptomyces* cultures, it will naturally be asked whether there are marked differences in the cytostatic activity of these actinomycins. From animal experiments it was discovered that there are indeed such differences, although they do not appear to be significant. For this reason, we have attempted to obtain derivatives of actinomycins in the hope of finding one which has a better carcinolytic activity than the actinomycins.

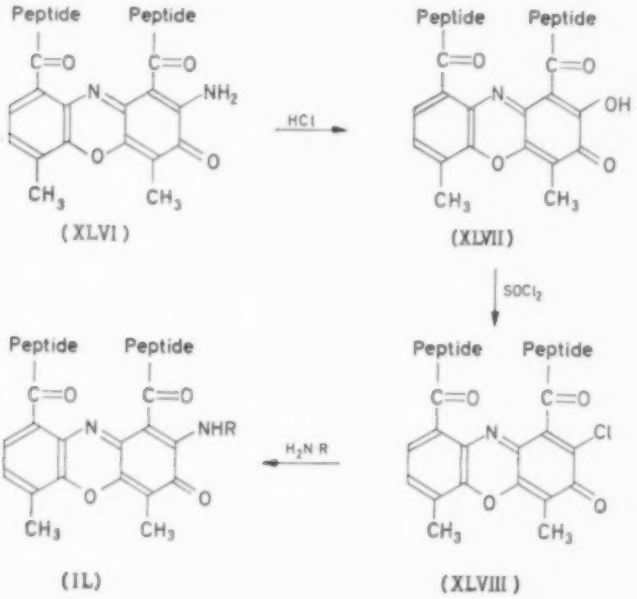
Derivatives of the actinomycins may be obtained in two ways: firstly, by modifying the peptide part, and secondly, by modifying the chromophore. Thus far, we have obtained derivatives in which the peptide part is modified only from the actinomycins $X_{0\beta}$ and $X_{0\delta}$, which, as already mentioned, contain hydroxy-proline or allo-hydroxy-proline. Both these actinomycins possess a free hydroxyl group (in either the hydroxy-proline or allo-hydroxy-proline unit) which can be esterified with acids. On the assumption that



(XLV)

the hydroxy-proline or allo-hydroxy-proline is located in that peptide group which is bonded to the benzoid ring of the chromophore, the esters of actinomycin $X_{0\beta}$ and actinomycin $X_{0\delta}$ may be represented by the formula (XLV), in which R represents the acid residue. With acetic acid and palmitic acid, we obtained the acetates and palmitates of actinomycins $X_{0\beta}$ and $X_{0\delta}$. These derivatives have less antibiotic and cytostatic activity than the parent actinomycins. Esterification was also effected with dicarboxylic acids, amino-acids and phosphoric acid. The esters thus obtained have a greater solubility in water than the actinomycins used as starting material, but their cytostatic activity has still to be determined.

Except for a few cases still under investigation, the only modifications of the chromophore that we have been able to effect are associated with the amino group. The derivatives which we have obtained were prepared in a manner which is summarized by the formulae (XLVI)–(XLVIII).

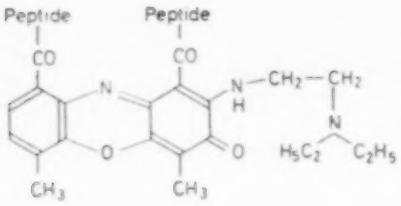


(XLVI) (XLVII) (IL) (XLVIII)

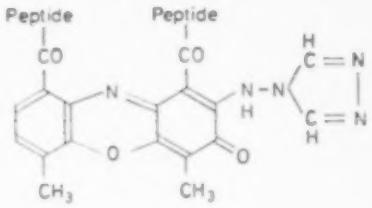
If an actinomycin (XLVI) is treated under mild conditions (four hours at 30°C) with 10 per cent hydrochloric acid, one molecule of ammonia is split off and a desamino-actinomycin (XLVII) is formed in almost quantitative yield[25]. During this process the peptide groups remain intact. In contrast to the actinomycins, the desamino-actinomycins have no toxic, antibiotic or cytostatic activity.

We have found that chlorine may be substituted for the hydroxyl group of the chromophore of the desamino-actinomycins (XLVII) by treatment with thionyl chloride. In this way crystalline antibiotically inactive chloro-actinomycins (XLVIII) are obtained[26]. If a chloro-actinomycin is treated with ammonia, the original actinomycin is recovered[26].

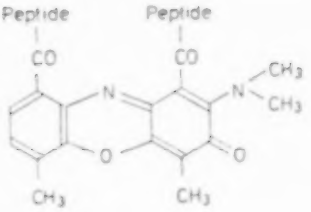
The chloro-actinomycins can be treated with primary and secondary amines instead of ammonia[26] to yield actinomycin derivatives in which one (IL) or both of the hydrogen atoms of the amino group of the chromophore have been replaced by alkyl groups or other residues. In this way we have prepared a number of derivatives whose biological activity is still under investigation[27]; (L)–(LIII) are the formulae of four such derivatives.



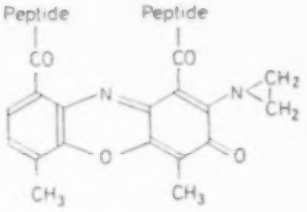
(L)



(LI)



(LII)



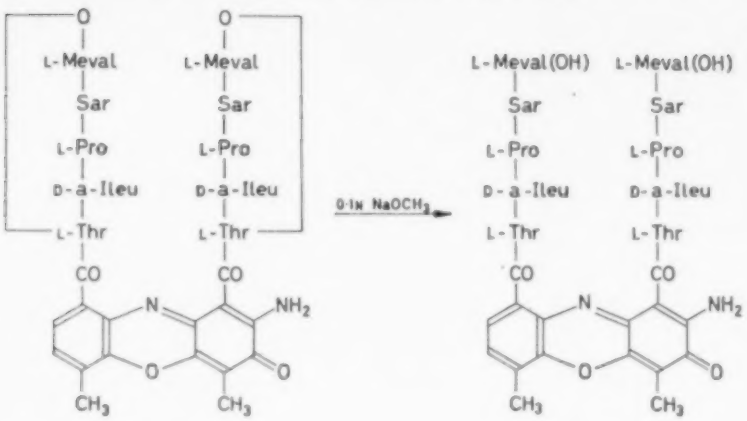
(LIII)

The dimethyl compound (LII) has only low antibiotic and carcinolytic activity. The *N*-diethylamino-ethyl derivative (L) also has less antibiotic and cytostatic activity than actinomycin C_3, but whether its therapeutic index is better than that of actinomycin C_3 remains to be determined. The same is true for the triazolyl derivative (LI). The most promising of the four derivatives seems to be *N*-dimethylene-actinomycin (LIII). In tumour experiments, its therapeutic index is better than that of the actinomycin C_3, a result that has encouraged us to make this derivative available for clinical trials. Its antibiotic activity is less than that of the actinomycin C_3, however.

The modifications of the peptide groups and the chromophore described above are limited by the fact that all the reactions involved must be carried out under conditions which do not destroy the peptide groups or the chromophore. From the very beginning it was obvious that this limitation would be overcome if the actinomycins and their derivatives could be prepared by synthesis. During the last three years we have been attempting to achieve this, and very recently we have been successful in synthesizing actinomycin C_3.

Our first attempt to synthesize actinomycin C_3 was based on the fact that the lactone groups of the actinomycin C_3 (LIV) are hydrolyzed by dilute sodium methoxide. The resulting actinomycin C_3 acid can be given the formula (LV). From our work on the synthesis of actinocinyl-peptides,

VOL. 2 1961

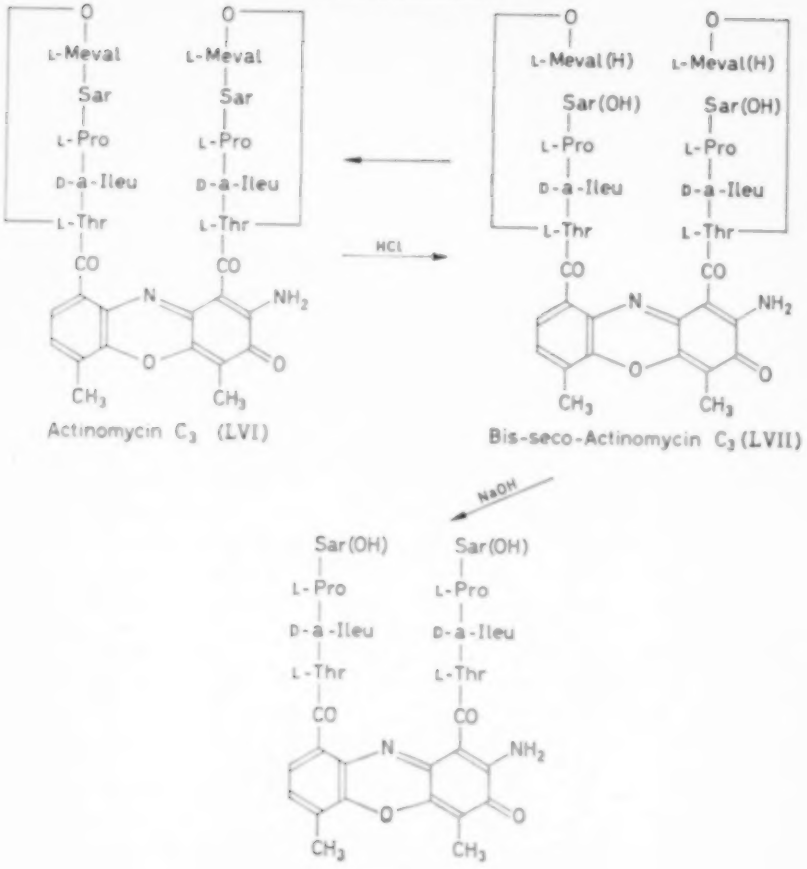


(LIV) (LV)

we had formed the opinion that it would not be too difficult to synthesize the actinomycin C_3 acid (LV), which is an actinocinyl-bis-pentapeptide. Our plan, therefore, was to carry out such a synthesis, and then to cyclize the two peptide chains of the actinomycin C_3 acid by esterification of the terminal carboxyl groups with the hydroxyl groups of the threonine residues. As this cyclization was expected to be the main difficulty in the synthesis, we decided to carry out an initial study with the actinomycin C_3 acid prepared from actinomycin C_3, and not with the precious synthetic material. However, experiments to prepare sufficient starting material for this purpose showed that the opening of the lactone rings was accompanied by side reactions, and that the resultant by-products could not be separated easily.

While these experiments were under way, Dr Sunderkötter in our laboratory made an observation which opened up a new route for the synthesis of actinomycin C_3. By treating actinomycin C_3 (LVI) with concentrated hydrochloric acid for four hours at 40°C, Sunderkötter obtained a degradation product which he found to have the formula (LVII)[29]. This product we have named bis-seco-actinomycin C_3. Its formation shows that concentrated hydrochloric acid attacks the peptide chains of the actinomycin preferentially at the bond between sarcosine and the *N*-methyl-valine. On mild treatment with sodium hydroxide, the bis-seco-actinomycin C_3 is converted into the actinocinyl-peptide (LVIII), which was synthesized in our laboratory by Lackner.

Bis-seco-actinomycin C_3 (LVII), contains the tetrapeptide L-threonyl-D-allo-isoleucyl-L-prolyl-sarcosine, in which the amino group is blocked by a carboxyl group of the chromophore but in which the carboxyl group is free. In addition to this tetrapeptide, the bis-seco-actinomycin C_3 contains *N*-methyl-valine with the methylamino group free but with the carboxyl group esterified with the hydroxyl group of the threonine residue. In other words, the molecule of bis-seco-actinomycin C_3 contains the two reactive groups necessary for a peptide synthesis.

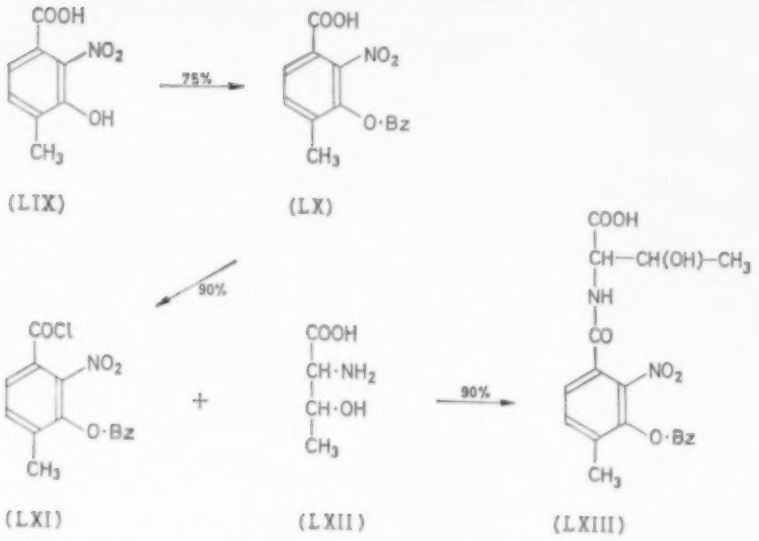


(LVIII)

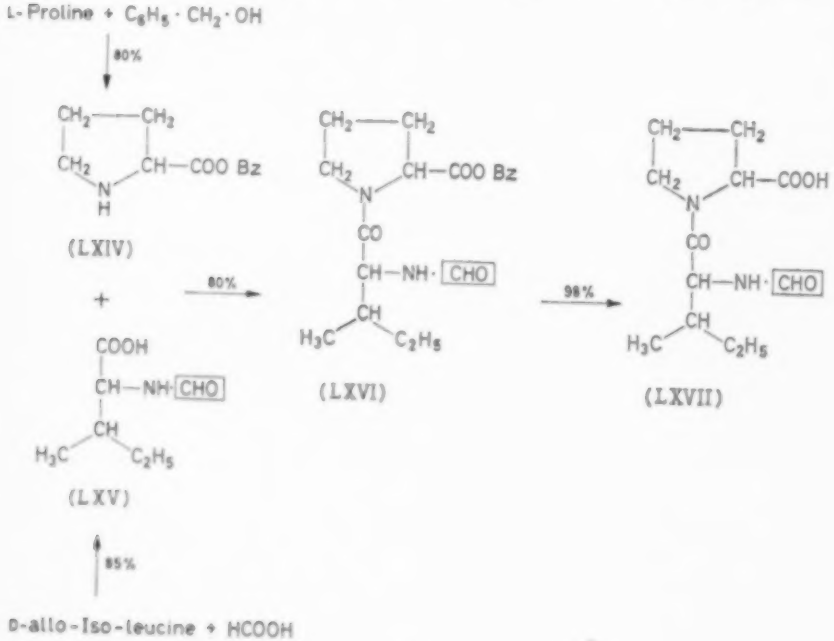
It was to be expected, therefore, that reagents producing peptide bonds would make it possible to couple the carboxyl group of the sarcosine with the methylamino group of the *N*-methyl-valine, and thus to regenerate the original actinomycin that was used to prepare the bis-seco-actinomycin. As Dr Ohly and Dr Sunderkötter in our laboratory have found[30], this reaction can be carried out either with cyclohexyl-carbodiimide, following Sheehan's method, or with ethyl chloroformate. By means of these reagents, they obtained crystalline actinomycin C_3 (LVI) in a yield of about 2·5 per cent from bis-seco-actinomycin C_3 (LVII).

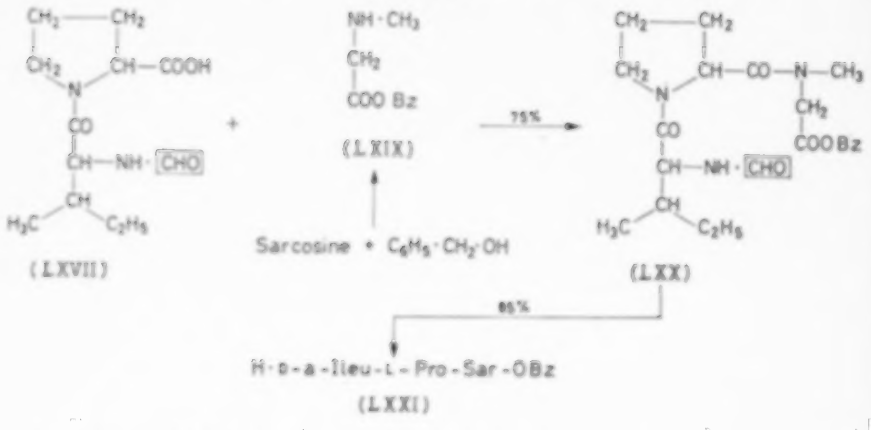
In this way a partial synthesis of actinomycin C_3 had been achieved. To develop this partial synthesis into a total synthesis, we had to synthesize the bis-seco-actinomycin C_3. This problem was solved in our Institute by Lackner[31]. The separate steps of this synthesis are illustrated by the formulae (LIX)–(LXXIV). 2-Nitro-3-hydroxy-4-methyl-benzoic acid (LIX) was benzylated at the hydroxyl group to give the compound (LX), which was chlorinated by means of thionyl chloride to give the chloride

VOL. 2 1961



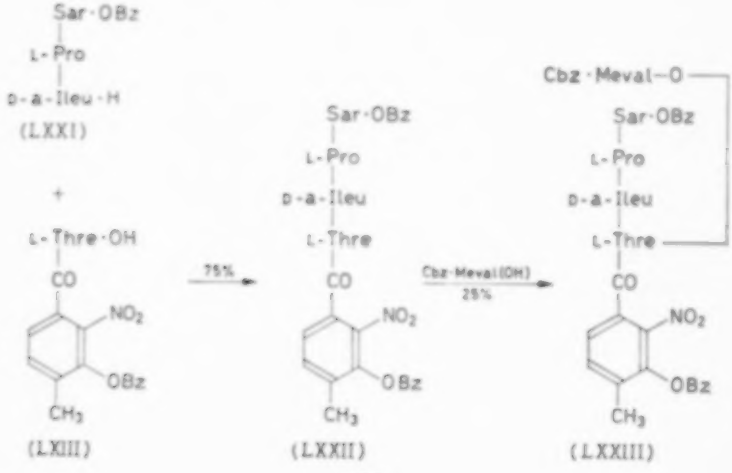
(LXI). Coupling of this chloride with L-threonine (LXII) in dilute sodium hydroxide gave the compound (LXIII). The carboxyl group of the compound (LXIII) was then coupled with the amino group of the benzyl ester (LXXI) of the tripeptide D-allo-isoleucyl-L-prolyl-sarcosine. The synthesis of this tripeptide-benzyl ester is illustrated by the formulae (LXIV)–(LXXI). L-Proline was esterified with benzyl alcohol to give L-proline-



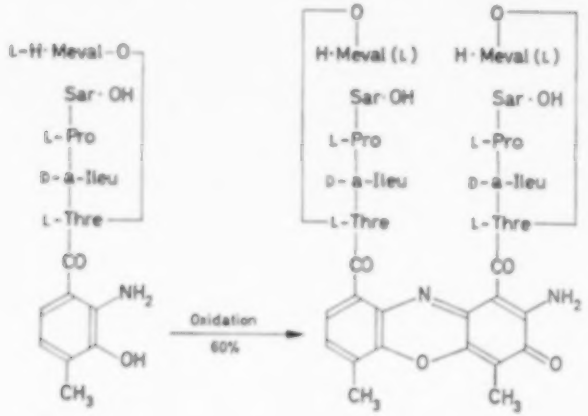


benzylester (LXIV), and D-allo-isoleucine was formylated to give formyl-D-allo-isoleucine (LXV). Coupling of the compound (LXIV) with the compound (LXV) by means of dicyclohexyl-carbodiimide yielded the compound (LXVI). The benzyl group was removed from the carboxyl group of this compound by catalytic hydrogenolysis, and the resulting formyl-D-allo-isoleucyl-proline (LXVII) was coupled with sarcosine benzylester (LXIX) (which was obtained from sarcosine by esterification with benzyl alcohol) to give the tripeptide derivative (LXX). Mild hydrolysis of this compound by means of hydrochloric acid in benzyl alcohol removed the formyl group from the amino group of the D-allo-isoleucine residue, thus giving D-allo-isoleucyl-L-prolyl-sarcosine benzylester (LXXI).

This tripeptide ester (LXXI) was then coupled with the L-threonine derivative (LXIII) to give the compound (LXXII). The next step was the esterification of the hydroxyl group of the threonine residue in compound (LXXII) with *N*-carbobenzoxy-methyl-valine, a reaction that could not be



accomplished by conventional methods of esterification. The desired result was finally achieved by using the *N,N*-carbonyl-diimide reagent first introduced for esterification by Staab[32]. The compound (LXXIII) thus obtained was hydrogenated in order to reduce the nitro group and to split off the two benzyl groups and the carbobenzoxy group. The reduction



product (LXXIV) thus formed was then oxidized by means of potassium ferricyanide in phosphate buffer at pH 7·3. In this way we obtained a mixture of different products from which we were able to separate by means of partition chromatography a compound (LVII) that had the same R_F value, the same spectrum, the same functional groups, and the same amino- and methylamino-acid content as the bis-seco-actinomycin prepared from actinomycin C_3. The best proof of the identity of the two compounds, however, was the fact that, by treatment with ethyl chloroformate, the synthetic compound (LVII) was converted into a crystalline, yellow-red, antibiotically active compound that was identical in every respect with actinomycin C_3 (LVI).

There is no doubt that the other actinomycins can be synthesized in the same way as actinomycin C_3. Moreover, it should now be possible to synthesize actinomycins and chromopeptides having chromophores and peptide parts different from those of the actinomycins we have at present. Perhaps among such compounds one will be found that has a better cytostatic activity than the actinomycins and actinomycin derivatives known at the present time.

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VOL. 2 1961

RECENT INVESTIGATIONS ON SOME ALKALOIDS FROM INDIAN PLANTS

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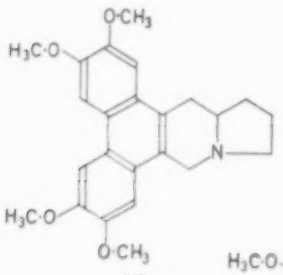
The study of alkaloids constitutes one of the most interesting branches of the chemistry of natural products. India is endowed with a very rich flora, and the ancient Indian system of medicine is largely based on plant remedies. Alkaloids have been isolated from many Indian plants reputed to have medicinal value, but attempts at structure elucidation have not been made in a number of cases. On closer examination, some of these have proved to be identical with alkaloids of known structure, as, for example, " toddaline " with chelerythrine[1], " biflorine " with protopine[2], " umbellatine " with berberine[3], " neprotine " with jatrorrhizine[3], " thalictrine " with magnoflorine[4] and " budrungine " with evodiamine[5]. In some other cases, however, there has been scope for structural investigations, and this paper is concerned with some of the results obtained in these studies.

Tylophora asthmatica Wight et Arn. is a perennial climber growing widely in the plains of India and is particularly abundant in the shrub jungles near Madras. The leaves of this plant have been used as an efficient substitute for ipecacuanha. From this plant Ratnagiriswaran and Venkatachalam[6] isolated two crystalline alkaloids, tylophorine and tylophorinine, which were characterized through a number of derivatives and assigned the molecular formulae $C_{24}H_{27}O_4N$ and $C_{23}H_{27}O_4N$ respectively. As a result of our



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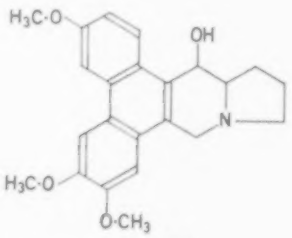

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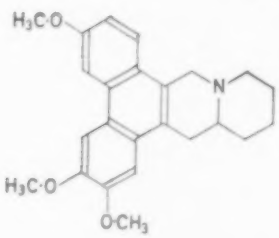


(III)

studies, tylophorine[7] has been shown to have structure (I) and tylophorinine[8] structure (II). The marked similarity of these structures to that of the alkaloid cryptopleurine (III)[9] obtained from *Cryptocarya pleurosperma* is of especial interest, because *Tylophora asthmatica* (Asclepiadaceae) belongs to the Order Tubiflorae of the Metachlamydeae, and is taxonomically far removed from *Cryptocarya pleurosperma* (Lauraceae), which belongs to the Order Ranales of the Archichlamydeae. The structure of cryptopleurine was determined by X-ray crystallography[10], without recourse to chemical studies, and salient features of our degradative studies leading to assignment of structures (I) and (II) to tylophorine and tylophorinine may, therefore, be of some interest.

The major alkaloid tylophorine, for which the correct molecular formula had been assigned by earlier workers, was found to contain four methoxyl groups but no *N*-methyl group. On Hofmann degradation, tylophorinemethine ($C_{25}H_{29}O_4N$) was formed, which on a second Hofmann degradation yielded the basic de-*N*-methyltylophorinemethine ($C_{26}H_{31}O_4N$) and a nitrogen-free product, obviously formed by the replacement of a dimethylamino group by hydroxyl. These results offered conclusive proof that the nitrogen atom in tylophorine was common to two rings.

On standing in acid solution, tylophorinemethine, a tertiary base, reverted to a quaternary form, the iodide of which was isolated and found to be identical with racemic tylophorine methiodide. Reversion of a methine to the inactive form of the quaternary salt from which it is derived has been observed in the case of quinolizidine alkaloids of the canadine type[11]. Such a trans-annular interaction is characteristic of eight-, nine- and ten-membered rings[12]. It may, therefore, be concluded that tylophorinemethine has an eight-, nine- or ten-membered ring incorporating the nitrogen atom.

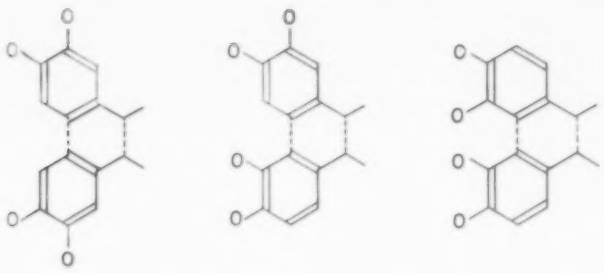
Treatment of tylophorine with cyanogen bromide gave a high yield of a neutral bromocyanamide, which was easily converted into a diethylaminocyanamide on treatment with diethylamine. Since tylophorine has no easily reducible unsaturated bonds, the ready cleavage of a carbon–nitrogen bond indicated[13] the presence of an Ar—C—N— system, and the high reactivity of the bromocyanamide pointed to the presence in it of a $—CH_2Br$ group; hence the partial feature Ar—CH_2—N— should be present in the alkaloid. The bromocyanamide could be converted into a hydroxycyanamide which regenerated tylophorine on acid hydrolysis. The ring opened up by cyanogen bromide should, therefore, be five- or six-membered.

Emde degradation of tylophorine methochloride yielded iso-dihydrohomotylophorine, $C_{25}H_{31}O_4N$. This, on dehydrogenation with palladized charcoal, gave the non-basic detetrahydro-iso-dihydrohomotylophorine, which showed positive pine splinter and Ehrlich tests. That no alteration in ring size had taken place was shown by reduction to the original Emde base. These experiments established the presence of a five-membered nitrogen-containing ring in tylophorine.

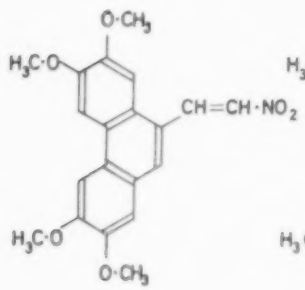
The ultra-violet light absorption spectra of tylophorine and the products derived from it by the Hofmann and the Emde degradations were all closely similar to that of phenanthrene. The presence of a phenanthrene ring was proved, and the orientation of the methoxyl groups in the alkaloid established, by the following experiments. iso-Dihydrohomotylophorine-

VOL. 2 1961

methine was oxidized with potassium permanganate, and the acidic fraction was esterified with diazomethane to yield a monoester, $C_{21}H_{22}O_6$, and a diester, $C_{22}H_{22}O_8$. Hydrolysis and decarboxylation of the monoester yielded a compound, $C_{19}H_{20}O_4$, corresponding to a tetramethoxymethylphenanthrene. Identification of this compound was rendered possible by a consideration of certain biogenetic aspects. Sir Robert Robinson[14] has suggested that the phenanthrene ring in cryptopleurine could have been



formed from two phenylalanine units. It seemed likely that tylophorine could have resulted from two dihydroxyphenylalanine units (or their equivalent) by coupling in one of three ways. Three of the four tetramethoxymethylphenanthrenes corresponding to these modes of fusion were synthesized, and the decarboxylation product was found to be identical with



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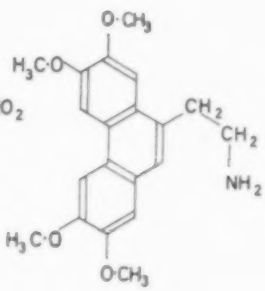

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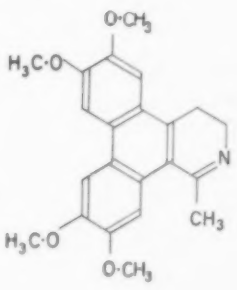

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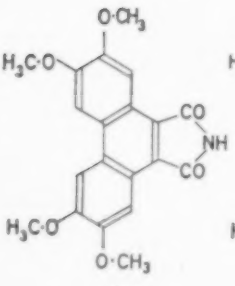

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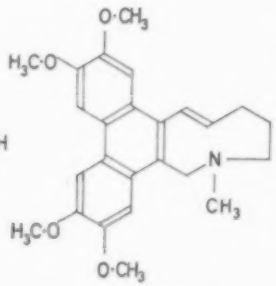

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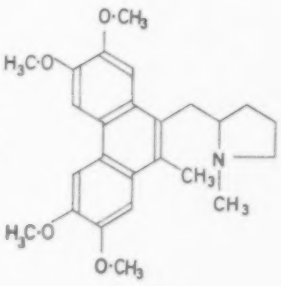
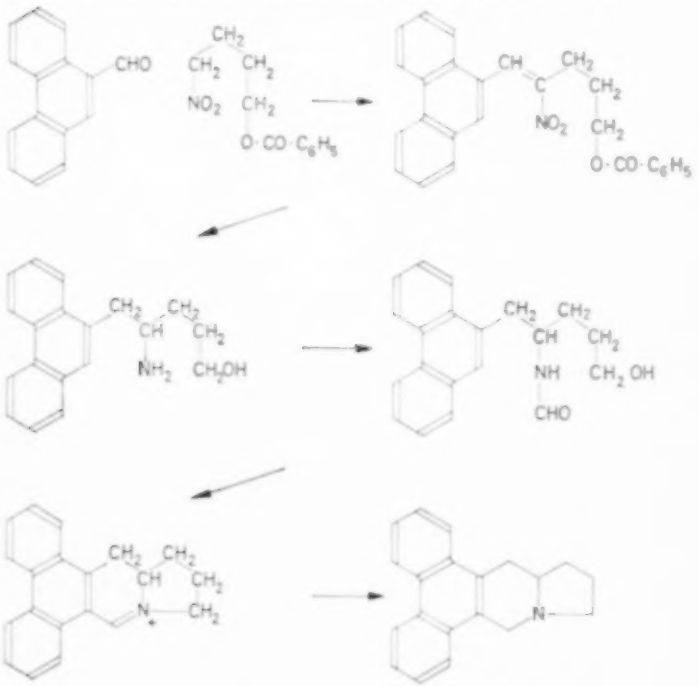


(IX)

2,3,6,7-tetramethoxy-9-methylphenanthrene, thus proving the presence of a phenanthrene ring, the orientation of the methoxyl groups, and one point of attachment of the heterobicyclic system in tylophorine.

The diester, $C_{22}H_{22}O_8$, referred to earlier, could be hydrolysed to a dicarboxylic acid which was readily converted into an anhydride and an imide. The latter was also obtained in poor yield by direct oxidation of tylophorine iso-methohydroxide. Several attempts to synthesize 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylic acid were made, in particular by oxidation of 2,3,6,7-tetramethoxy-9,10-dimethylphenanthrene under a variety of conditions; all these efforts were unsuccessful, however, the starting material being either recovered or totally destroyed. Ultimately, 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylimide was synthesized as follows. Condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde with nitromethane yielded the corresponding 9-(2′-nitrovinyl)-phenanthrene (IV); this compound was reduced by lithium aluminium hydride to 2,3,6,7-tetramethoxy-9-(2′-aminoethyl)-phenanthrene (V), whose acetyl derivative, on cyclization with phosphorus oxychloride, gave the dihydroisoquinoline (VI). Oxidation of the methiodide of (VI) with potassium permanganate yielded the required imide (VII), which was identical (mixed melting point and infra-red light absorption spectrum) with the oxidation product from tylophorine iso-methohydroxide.

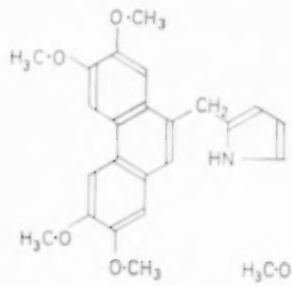
Chart 1. Synthesis of phenanthro-(9,10: 6′,7′)-indolizidine (X)



VOL. 2 1961

On the basis of these results, tylophorine was uniquely formulated as 2,3,6,7-tetramethoxyphenanthro-(9,10: 6′,7′)-indolizidine (I), tylophorinemethine as (VIII), and iso-dihydrohomotylophorine as (IX).

In order to serve as a model for the synthesis of tylophorine, synthesis of the parent ring system, phenanthro-(9,10: 6′,7′)-indolizidine (X), was carried out by the sequence of steps shown in *Chart 1*. However, this method could not be applied to the synthesis of tylophorine itself, since 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde, on condensation with δ-nitrobutyl benzoate, yielded a complex mixture of as yet unidentified products but not the desired nitropentene. Nor could Marchini and Belleau's method[15] for the synthesis of cryptopleurine be applied, since 2,3,6,7-tetramethoxy-9-phenanthrylmethyl chloride failed to condense with proline ester, self-condensation of the latter apparently proceeding much faster than the reaction with the halide. Ultimately, success was achieved by the following route. Treatment of pyrryl magnesium bromide with 2,3,6,7-tetramethoxy-9-phenanthrylmethyl chloride yielded 2-(2,3,6,7-tetramethoxy-9-phenanthrylmethyl)-pyrrole (XI). Reduction in acetic acid solution in the presence of Adams catalyst gave the corresponding pyrrolidine (XII),



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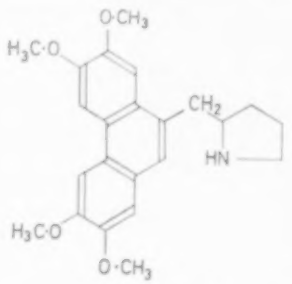
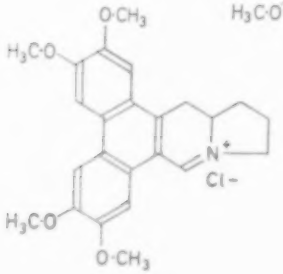


(XII)



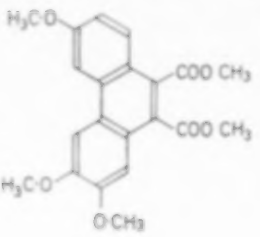
(XIII)

whose *N*-formyl derivative, on cyclization with phosphorus oxychloride, yielded the quaternary chloride (XIII). This was reduced by sodium borohydride to (±)2,3,6,7-tetramethoxyphenanthro-(9,10: 6′,7′)-indolizidine (I). The infra-red light absorption spectrum of the synthetic compound was identical with that of (−)tylophorine in chloroform solution. The synthetic compound was resolved by means of camphor sulphonic acid into (−)tylophorine, m.p.289°(d), $[\alpha]_D^{30}$ − 11·5°, and (+)tylophorine, m.p.289°(d), $[\alpha]_D^{30}$ + 12·25°. The structure (I) assigned to tylophorine was thus proved both by degradation and by synthesis.

The minor alkaloid tylophorinine required elaborate treatment for purification, and, on the basis of analyses of the pure material, the molecular

formula had to be revised to $C_{23}H_{25}O_4N$. The alkaloid contained three methoxyl groups and the infra-red light absorption spectrum showed a weak band at 3·1μ indicating a hydroxyl group. The ultra-violet light absorption spectrum was very similar to that of cryptopleurine, and was unchanged on the addition of alkali, showing that the hydroxyl group was not phenolic. Acetylation yielded an acetate, with infra-red light absorption bands at 5·8 and 8·0μ, confirming the presence of a hydroxyl group.

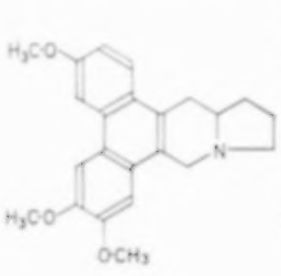
Mild oxidation of tylophorinine methiodide yielded an acid, which was converted into an anhydride under crystallization conditions. Methylation of the acid with diazomethane yielded a diester, $C_{21}H_{20}O_7$, m.p.160–162°, which was identical with dimethyl 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylate (XIV), obtained similarly from cryptopleurine, kindly pre-



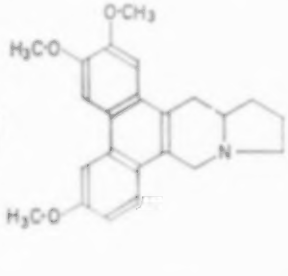
(XIV)

sented to us by Dr Gellert. This established the presence in tylophorinine of a 2,3,6-trimethoxyphenanthrene moiety, to whose 9,10-positions the heterocyclic portion of the molecule was linked. Since less than a gram of material was available, and the Hofmann and Emde degradations gave very poor yields, further work on the lines employed in the case of tylophorine was not possible. However, a definite assignment of structure was made possible through the following experiments. Catalytic hydrogenation of tylophorinine in acetic acid solution in the presence of palladized charcoal and perchloric acid yielded desoxytylophorinine, $C_{23}H_{25}O_2N$.

On the assumption that tylophorinine contained a phenanthro-indolizidine system like tylophorine, two structures, (XV) and (XVI), were possible for desoxytylophorinine. The synthesis of the structure corresponding to (XV) was effected on lines analogous to that employed for tylophorine,



(XV)



(XVI)

starting from 2,3,6-trimethoxy-9-phenanthrylmethyl chloride. The infra-red light absorption spectrum in chloroform solution of the synthetic compound was identical with that of desoxytylophorinine obtained from the natural alkaloid, and both substances gave the same methine, $C_{24}H_{27}O_3N$, m.p.171·5° (identical melting point, mixed melting point, and infra-red light absorption spectra) on Hofmann degradation.

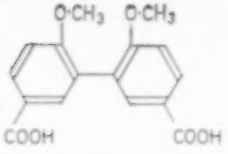
Hydrogenolysis of tylophorinine to desoxytylophorinine under the conditions employed indicated the presence of a benzyl alcohol system. Since tylophorinine does not show the properties of a carbinolamine, the hydroxyl group could be uniquely located and tylophorinine itself assigned structure (II).

Tylophorine and tylophorinine are the only two alkaloids known at present which are phenanthroindolizidines. The Asclepiadaceae are a large family of some 1,800 species, there being a record of 140 species in India alone. Further search in this family may bring to light many more alkaloids of this type.

The Menispermaceae are one of the families of which quite a large number of species has been examined for alkaloids. While protoberberines and aporphines have been isolated from some, the predominant type found in this family is the biscoclaurine type of which more than thirty alkaloids are known at present[16]. In India, there is a record of only eleven genera and eighteen species belonging to the Menispermaceae. The isolation of tiliacorine from *Tiliacora racemosa* Colebr. has been reported by various workers[17], who have recorded for the alkaloid different melting points and analyses. Tiliacorine was isolated by us by a modified procedure and purified by chromatography, and gave analyses corresponding to $C_{34}H_{29}O_3N_2(OCH_3)_3$. The alkaloid was soluble in Claisen's alkali, indicating the presence of a hindered phenolic hydroxyl group. The ultra-violet light absorption spectrum was very similar to that of trilobine and dihydromenisarine ($\lambda_{max} = 295$ mμ, log $\epsilon = 3{\cdot}91$; $\lambda_{min} = 265$ mμ, log $\epsilon = 3{\cdot}48$).

With a mixture of sulphuric and nitric acids, the alkaloid gave the same characteristic blue colour as trilobine, menisarine and isotrilobine, indicating the presence of a dibenzodioxin system[18]. Conventional procedures[16] which were applied in the case of biscoclaurine alkaloids (such as Hofmann degradation followed by ozonolysis, or cleavage with sodium and liquid ammonia) failed to yield any useful result. However, direct oxidation studies were fruitful, and made it possible to assign a structure to tiliacorine[19, 20].

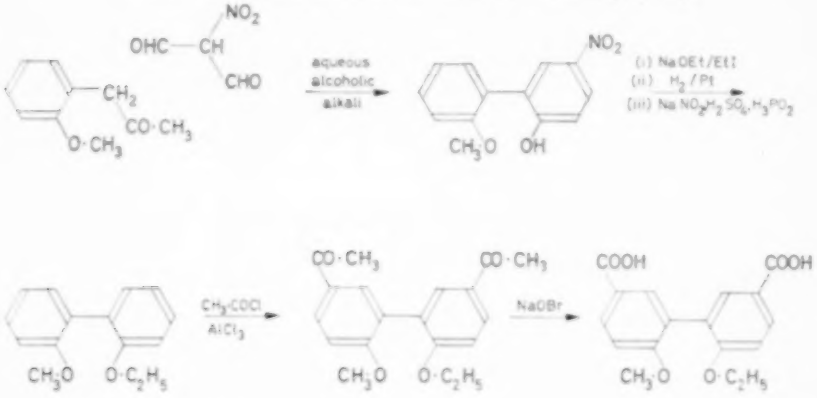
Oxidation of *O*-methyltiliacorine dimethiodide with potassium permanganate yielded an acid, $C_{16}H_{14}O_6$, which gave a dimethyl ester, $C_{18}H_{18}O_6$. This was surprising, since all known biscoclaurine alkaloids containing a dibenzodioxin system yield only 2-methoxydiphenyl ether 4′,5-dicarboxylic acid, $C_{15}H_{12}O_6$. The acid, $C_{16}H_{14}O_6$, contained two methoxyl groups, and could not have been a dimethoxydiphenyl ether dicarboxylic acid which would have had the formula $C_{16}H_{14}O_7$. Decarboxylation of the acid, $C_{16}H_{14}O_6$, yielded a compound, $C_{14}H_{14}O_2$. The ultra-violet light absorption spectrum and the formula of this substance suggested that it could be 2,2′-dimethoxydiphenyl, and this was confirmed by comparison with an



(XVII)

authentic sample. If tiliacorine is a biscoclaurine type alkaloid, the point of attachment of the diphenyl to the rest of the molecule should be through the 5- and 5′- positions. Consequently, the acid, $C_{16}H_{14}O_6$, should be 2,2′-dimethoxy-5,5′-dicarboxydiphenyl (XVII), and this was confirmed by direct comparison of the acid and its dimethyl ester with authentic specimens[19].

Chart 2. Synthesis of 2-methoxy-2′-ethoxy-5,5′-dicarboxydiphenyl



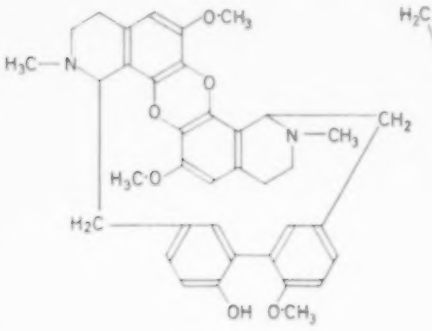
The isolation of 2,2′-dimethoxy-5,5′-dicarboxydiphenyl clearly indicates that tiliacorine is derived from two molecules of coclaurine, the carboxyl groups at the 5,5′-positions labelling the points of attachment of the diphenyl system to the two isoquinoline moieties. Tiliacorine is thus revealed as a new type of biscoclaurine alkaloid in which the benzyl residues of the two coclaurine units are linked directly, and not through oxygen as is the case in all instances recorded so far. Numerous examples of such a phenol coupling are known, the aporphines being a familiar example[21]. The surprising thing, therefore, is not the direct coupling between the two benzyl moieties observed in tiliacorine, but that such a type has not been encountered so far, although the chemical examination of over fifty species of Menispermaceae and Magnoliaceae is on record.

Oxidation of tiliacorine dimethiodide itself yielded 4-methoxyisophthalic acid. This indicated the location of the phenolic hydroxyl group in the diphenyl unit, and this assignment was confirmed by the formation of 2-methoxy-2′-ethoxy-5,5′-dicarboxydiphenyl on oxidation of *O*-ethyltiliacorine dimethiodide[20]. An authentic specimen of this acid was synthesized by a novel method, illustrated in *Chart 2*, which utilized nitromalonaldehyde,

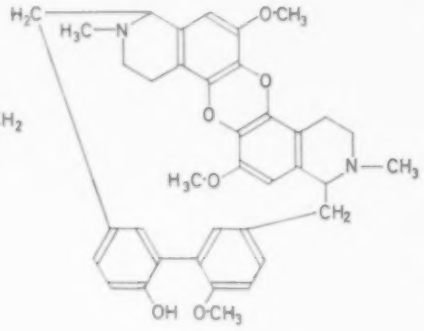
VOL. 2 1961

in a manner similar to that used by Hill and Hale many years ago for the synthesis of *p*-nitrophenol derivates[22].

Analytical results are in agreement with the presence in tiliacorine of a dibenzodioxin ring, which was indicated by the colour reaction, and also with the location of two of the methoxyl groups in this unit. With these considerations in mind, and on the basis of the Faltis theory[23], tiliacorine could almost certainly be formulated as (XVIII). The alternative structure (XIX), involving the 5,6-positions of the isoquinoline moieties, is of a type that has not been encountered in Nature so far.

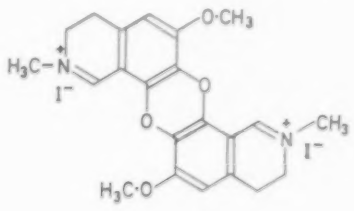


(XVIII)



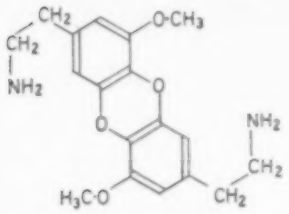
(XIX)

It was necessary to degrade tiliacorine to an identifiable dibenzodioxin derivative, so that the presence of this ring system in the alkaloid, and the orientation of the substituents suggested in structure (XVIII), could be unequivocally established. With this object, tiliacorine was oxidized with manganese dioxide–sulphuric acid[24] to yield a compound which was isolated as the quaternary iodide, $C_{22}H_{24}O_4N_2I_2$, and which can be formulated as (XX) on the basis of structure (XVIII) for tiliacorine. Since



(XX)

the oxidation with manganese dioxide gives very poor yields, further degradation based on the oxidation product has not been feasible. It is hoped that it will be possible to prove structure (XX) for the quaternary iodide by synthesis. The amine (XXI), has been synthesized, and this is expected to lead not only to the quaternary iodide (XX), but ultimately to the synthesis of the alkaloid itself.

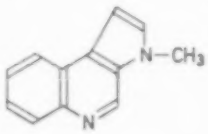


(XXI)

The Apocyanaceae are a large family rich in alkaloid-bearing plants, as is seen from the fact that no less than two hundred of the thousand and more alkaloids known at present have been obtained from plants belonging to this family[25]. Though steroidal alkaloids have been found in certain genera, the majority of Apocyanaceous plants so far investigated yield indole alkaloids of greater or lesser complexity. The presence of alkaloidal material in *Alstonia scholaris*, a tall graceful tree growing all over India, has been known for nearly a century, but it was through the work of Goodson and Henry[26] that reliable data were first provided. These authors isolated the principal alkaloid, echitamine, as its "hydrochloride", and characterized it by preparation of several derivatives. They showed that it contained a carbomethoxy group, and, by means of colour reactions on the alkali-fusion products, demonstrated the presence of an indole nucleus. Recently, echitamine has aroused considerable interest[27a–e], and, while it is not possible to outline all the work carried out by the different groups of investigators, salient features can be summarized.

VOL. 2 1961

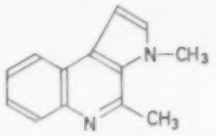
The alkaloid was easily recognized to be a dihydroindole derivative from its ultra-violet light absorption spectrum. The presence of an allyl quaternary ammonium system was established by reduction of echitamine chloride to a tertiary base, originally formulated by us as $C_{22}H_{28}O_3N_2$, but later shown to be $C_{21}H_{26}O_3N_2$ by Conroy *et al.*[27d]. The tertiary base gave an N_a-acetyl* derivative (colour reaction, infra-red and ultra-violet spectra), showing the presence of an $-N_aH$ group. Selenium dehydrogenation of the tertiary base yielded 1′-methylpyrrolo-(2′,3′:3,4)quinoline (XXII),



(XXII)

whole identity, surmised on the basis of its analysis and ultra-violet light absorption spectrum, was confirmed by comparison with an authentic specimen obtained by silver acetate oxidation of calycanthine. On zinc dust distillation of what was presumably the same tertiary base, Birch, Hodson and Smith obtained 1′,2-dimethylpyrrolo-(2′,3′:3,4)quinoline (XXIII).

* The nitrogen atoms in the molecule are designated N_a and N_b.

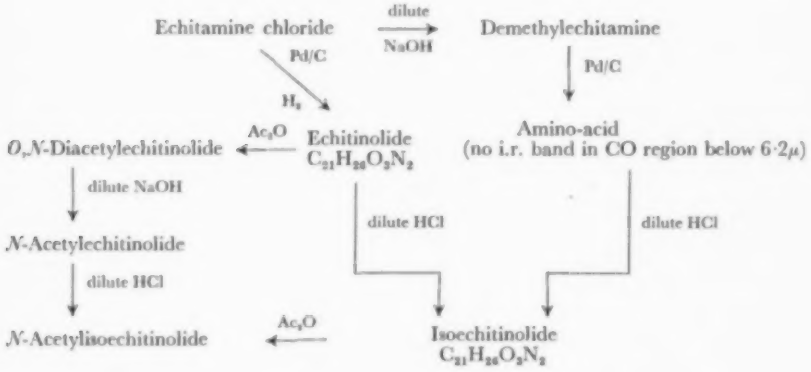


(XXIII)

In our attempts to formulate a structure for echitamine, we were largely guided by the work of Hodson and Smith[28] on the ultra-violet light absorption characteristics of dihydroindoles in neutral and in acid solution. When these observations were taken into account, the ultra-violet light absorption characteristics of echitamine and several products derived from it appeared to indicate the presence of an N_a—C—N_b system. Although the tertiary base, $C_{21}H_{26}O_3N_2$, obtained on reduction of echitamine chloride, did not undergo the reductive cleavage characteristic of eserine-like compounds, its methiodide underwent ring opening on treatment with cold 2N alkali to yield a compound, $C_{22}H_{30}O_4N_2$, which could be deoxygenated to a second tertiary base, $C_{22}H_{30}O_3N_2$. Any structure proposed for echitamine will not be acceptable unless it is capable of explaining these results*.

Some other experimental work having a bearing on the structure of echitamine carried out in our laboratory is shown in *Chart 3*. In order to avoid confusion, the terms " echitinolide " and " isoechitinolide ", suggested by Conroy *et al.*, have been adopted.

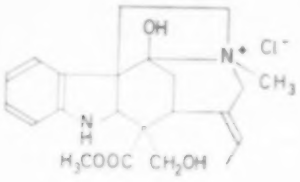
Chart 3. Synthesis of echitinolide, isoechitinolide, and their acetyl derivatives from echitamine



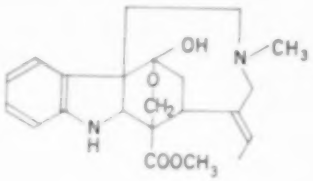
It was obvious that isoechitinolide must be a lactone, since it was obtained from demethylechitamine. The third oxygen atom must be present as an ether, since the compound was recovered unchanged after refluxing with sodium borohydride in methanol solution, and since it did not contain a

* See p. 437.

hydroxyl group, as shown by the absence of active hydrogen in *N*-acetyl-isoechitinolide. Furthermore, isoechitinolide did not also contain the double bond originally present in echitinolide, since its *N*-acetyl derivative was recovered after treatment with sodium periodate–osmium tetroxide. These results could not be satisfactorily explained on the basis of our original presumption that the reduction product of echitamine chloride was an ester. Indeed, we discovered that our "dihydroechitamine" was a lactone, since Zeisel determination showed no methoxyl group, and it should really be formulated as $C_{21}H_{26}O_3N_2$. At this stage, a paper by Conroy *et al.* appeared in which it was recognized that the initial product of reduction of echitamine is so consistituted as to lose spontaneously a molecule of methanol with the formation of a lactone. These authors also clearly established the presence of a $HOCH_2—\underset{|}{C}—COOCH_3$ moiety, and suggested the structure (XXIV) for echitamine chloride and (XXV) for echitamine



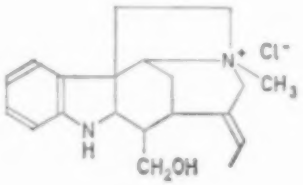
(XXIV)



(XXV)

base. The formation of alloechitamine, with the properties described for it, is not compatible with alternative structures. The sequence of reactions starting with echitinolide methiodide referred to earlier is also satisfactorily explained, since the system O—C—N present in echitinolide might be expected to simulate the behaviour of the N—C—N system present in eserine-like compounds.

Conclusive proof of the structure (XXIV) suggested for echitamine chloride could be provided by correlation with some compound of established structure, *e.g.* the alcohol (XXVI), obtained from the Wieland–Gumlich aldehyde[29].



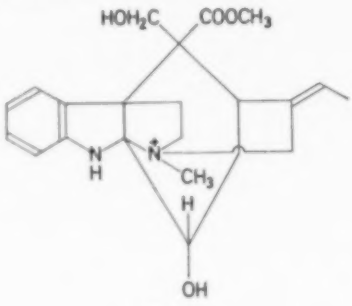
(XXVI)

In a recent survey[30], it has been estimated that hardly 2 per cent of the 191,000 species of flowering plants has been examined for alkaloids. The alkaloid chemist need never be at a loss for interesting problems, and there will always be enough around to beguile his wits.

VOL. 2 1961

Note added in proof

Professor J. M. Robertson and co-workers have solved the structure of echitamine by the X-ray method working on crystals of echitamine bromide methanol solvate[31]. *This structure (XXVII) has been confirmed independently by the X-ray investigations of crystals of echitamine chloride and iodide*[32].



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VOL. 2 1961

PHYSICOCHEMICAL METHODS OF INVESTIGATING NATURAL PRODUCTS

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INTRODUCTION

When one reflects on the achievements of organic chemists who studied natural products more than twenty-five years ago, one cannot fail to be increasingly impressed. Then, structural determination involved a lengthy programme of extraction and purification, chemical degradation and synthesis. In the determination of purity, or proof of identity, a few simple properties were available, such as melting point, boiling point, mixed melting point, refractive index, or specific optical rotatory power. Since that time, the introduction of new physical methods has revolutionized the subject and opened up a new era, not only by speeding up the work, but also by making it possible to deal with smaller quantities of material and by providing detailed information of a kind not previously obtainable, such as, for example, certain aspects of stereochemistry.

The variety and scope of these physical methods are now vast, and each has its own particular sphere of application. Although in some respects the information provided by one method simply confirms that obtained by another, it is usually desirable to have all available, since each has certain specific advantages.

EXTRACTION AND SEPARATION

The main applications of physical methods are: (1) for extraction, separation and purification; (2) for structural determination; and (3) for quantitative assay. The older, standard procedure of solvent extraction has been developed into the more powerful method of counter-current separation[1], in which differences in the distribution of solutes between two or more solvents are applied, greater volumes can be used, and repeated partition can be achieved by automatic and continuous mechanical operations. In this way, it has been possible to concentrate and extract such substances as hormones, vitamins, antibiotics and peptides[2].

Some compounds, expecially those of high molecular weight, are well suited to separation by electrophoresis[3]. This method is based upon the differences in mobility of charged colloidal particles under an electric field gradient, and commercial instruments are now available for the separation and estimation of very complex compounds.

Other methods of separation include molecular distillation, dialysis, sublimation and freeze-drying, diffusion, and ultracentrifugation. Most important of all, however, is chromatography of one kind or another[4]. Simple absorption chromatography has now been extended by the use of a large variety of column materials, such as metallic oxides, silica or silicic

acid, or cellulose. The use of more than one liquid phase in partition chromatography[5], and graded elution[6], has been much developed. A recent advance in this connection is the use of capillary columns[7], which make it possible to use much smaller quantities and to obtain sharper separation. The choice of column material and liquid phases is determined semi-empirically, although some general principles can be laid down with regard to the type of substances being separated. Paper chromatography has been improved in several ways, by using ascending flow, centrifugal methods[8], or electrophoresis, and by the use of automatic inspection devices. In many respects, however, and especially for volatile substances and when small quantities are involved, gas–liquid (vapour phase) chromatography has proved superior to other methods[9]. Here again, the choice of column material and liquid phase is somewhat empirical and is decided by the particular case. Recent developments have been mainly concerned with the outflow detector equipment. In a few cases, automatic titration can be used. Hot wire or thermistor detectors rely on the difference in thermal conductivity of different vapours, and the gas density balance has been developed to a high degree of sensitivity[10]. The electrical conductivity of a flame of burning hydrogen through which an organic vapour is passing has also been applied in the thermal ionization detector to give remarkable sensitivity[11]. In another very sensitive method[12], argon, used as the carrier gas, is excited to a metastable state by a radioactive source such as strontium-90 or krypton-85, and then ionizes organic vapours by collision, the amount of ionization being recorded by the current under a constant applied voltage. When the separation of radioactive molecules is involved, such as arises with compounds containing carbon-14, the effluent vapours can be made to excite a phosphor or scintillation counter, and the radiation thus emitted can then be detected continuously with a photoelectric multiplier[13]. All these devices detect and estimate the amount of the emerging vapours. An obvious advance for some purposes would be the simultaneous qualitative identification of the compounds. Recently, it has been suggested that differences in electron affinity of molecules might be used for this purpose[14], or at any rate to separate them into structural types.

VOL. 2 1961

X-RAY ANALYSIS

Of all the methods of structural determination, undoubtedly the most far-reaching in scope is X-ray diffraction by crystalline solids. In principle, it is capable of revealing the whole molecular structure, both the spatial atomic arrangement and the interatomic distances. X-rays are scattered by the electron clouds of atoms, and the intensity distribution in the diffraction pattern should, therefore, lead to an electron density contour map. Measurements in different dimensions will then serve to build up the entire structure, although, as a rule, the hydrogen atoms cannot be seen and must be inferred. A remarkable analysis by Friedrichson and Mathieson[15] established the formula of the alkaloid cryptopleurine without prior chemical information about the substance.

Very considerable computations have usually been necessary to obtain a fit between the observed pattern and an assumed molecular model. Yet this computation is not the only difficulty. Calculation of the intensity

pattern involves both the atomic structural amplitude factors and the corresponding phase angles. The latter cannot be determined directly, and this gives rise to what has been called the phase problem. If the main features of the structure are already known from chemical work, and the crystals are centrosymmetric, the problem can sometimes be solved without too much difficulty, but this is not usually the case. The difficulties may be avoided if one or more heavy atoms are present in, or can conveniently be introduced into, the molecule: according to the particularly heavy atom and type of crystal structure, the molecular structure can be solved more or less exactly. Rough rules have been suggested for the most desirable relative mass of the heavy atom. Another possible way of getting round the phase problem is by use of two or more isomorphous compounds.

Of course, in spite of these difficulties, the structure of many important molecules has been settled in recent years[16]. These include steroids, terpenes, antibiotics, alkaloids such as strychnine[17], colchicine[18] and calycanthine[19], natural pigments, proteins and nucleosides, and some progress has been made with viruses. Some of these determinations have been important in a wider sense. For example, in 1932 Bernal[20] first suggested that the structure assumed earlier for the main steroid skeleton in ergosterol was inconsistent with the X-ray pattern, and his results led to the formula which is now accepted. Subsequently, complete X-ray determinations have been carried out on cholesterol[21], calciferol[22] and lumisterol[23], in each case by use of a derivative containing a heavy atom. X-ray powder patterns are now available for a very large number of steroids as a guide to identity[24], supplementing other common properties if required. An exhaustive and refined X-ray analysis of penicillin[25], using several heavy atom salts, gave the conclusive evidence for the β-lactam structure; and the recent detailed solution[26] of the complex vitamin B_{12} (containing nearly 200 atoms) and other molecules studied by Hodgkin and her co-workers has shown the enormous power of the method. Very recently, remarkable results have been reported for myoglobin[27].

It seems likely that significant improvements in the technique will be made during the coming years, not only in diagnostic precision but also in the speed of computation. If the intensities are to be measured more accurately, Geiger or scintillation counters should replace photographic methods, although considerable labour will still be necessary. However, with more accurate intensity data and refinement of the Fourier analysis, hydrogen atoms may be more definitely located, and the new automatic computing instruments should speed up the whole operation.

It is certain, however, that, for reasons of convenience, other physical methods will be used for structural work for some time to come.

ULTRA-VIOLET ABSORPTION

Of the methods based upon optical transitions between molecular energy levels, visible or ultra-violet absorption in the region 7000–2000Å is perhaps the oldest. Absorption of electronic excitation energy is primarily involved, and, although the wavelength and intensity of the absorption band is fairly characteristic of the group of atoms forming the chromophore[28], it often happens that different structures absorb at about the same wavelength.

At present, the method is empirical, for it is impossible, in general, to calculate the values of molecular electronic energy states and the transition probabilities. The absorption is primarily a function of the electron space cloud, and the spectra are, therefore, far less characteristic of a nuclear skeleton than, for example, the infra-red absorption spectra. On the other hand, the distinctive properties of the ultra-violet absorption band systems sometimes provide a more direct indication of a class of compound than the vibrational spectra. An example of this is the differentiation of aliphatic and aromatic structures, or of saturated and unsaturated systems.

Saturated compounds, as a rule, do not absorb at wavelengths above 2000Å. Single chromophores such as C=C, C=O, S=O, NO_2 absorb in the ultra-violet, and the extinction coefficients vary over a wide range. They are sometimes so high that only very small (μg) quantities of material are needed to measure the absorption spectrum. Structural investigations rely not only on the fact that the rough position and intensity of the absorption bands may indicate the main chromophore, but also on the fact that the specific small variations in these properties may indicate the relationship of the key group to its particular environment. Factors which affect the position and intensity include the nature and position of neighbouring substituents, cumulation or conjugation, the size and type of the ring in which the chromophore occurs, steric factors and even other structural features such as stereochemical conformation. Solvents, too, have distinct effects, and more work on these would be valuable, not only to provide more reference data, but also as a possible additional means of diagnosis. Sometimes a particular chromophore absorbs weakly, but conversion into a convenient derivative leads to greatly intensified absorption. This occurs, for example, when a ketone is converted into its semicarbazone.

The introduction of photoelectric recording has greatly simplified the measurement of ultra-violet absorption spectra, and routine instruments using prisms or gratings, with single or double beam are now available. It is doubtful whether an extension of the conventional range into the vacuum ultra-violet below 2000Å will be profitable for general purposes, since, apart from other experimental difficulties, some of the usual solvents will cease to be usable. Also, since it is known that ultra-violet absorption spectra are sharpened up if measurements are made on substances in the form of solids at very low temperatures, it might be thought desirable to apply this method in structural work. Here again, however, it is unlikely that much will be gained in most cases, for the use of low temperatures tends to bring out detailed vibrational structure of an electronic band system, and for our present purpose this may be less important than the location of the main electronic absorption level.

Much work has concerned double or triple bond systems, especially when they are conjugated, since conjugation shifts the absorption to longer wavelengths. In polyenes, such as

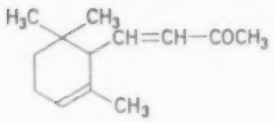
$$C_6H_5 \cdot (CH{=}CH)_n \cdot C_6H_5 \text{ or } CH_3 \cdot (CH{=}CH)_n \cdot COOH,$$

the position and intensity of absorption is determined by the length of the conjugated chain. This has been useful in the investigation of carotenoids, and in a similar way with polyacetylenes[29]. Thus, the very characteristic

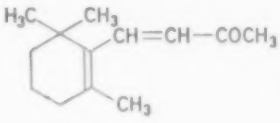
absorption of the triacetylene system in conjugation with a diene was used to establish the structures of isomycomycin (I)[30] and of mycomycin, and these are in accord with the equally characteristic infra-red absorption bands of these compounds. In β-ionone (III), the greater extent of conjugation compared with that in α-ionone (II) leads to absorption at longer wavelengths[31]. Similarly, it was possible to decide[32] in favour of the structure (IV) rather than (V) for patulin. The α,β-unsaturated ketonic side-chain

$$CH_3{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}COOH$$

(I)



(II)



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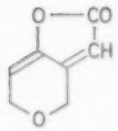

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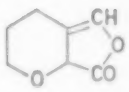
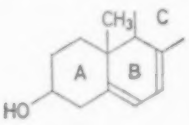


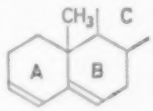
(V)

in helvolic acid can be identified[33], but some infra-red and nuclear magnetic resonance studies[34] have shown that the ultra-violet absorption spectrum does not provide the whole story.

In steroids containing two C=C double bonds, the location of the absorption band depends on whether these bonds are in the same or in different rings[35]. For example, ergosterol (VI) and cholesta-3,5-diene (VII) have absorption maxima at 2820Å and 2340Å respectively. Similarly, α, β-unsaturated ketones among the steroids can be distinguished.



(VI)



(VII)

With polynuclear aromatic ring systems[36], or with tropolones and azulenes, characteristic absorption occurs: as a general principle, the shift is to longer wavelengths as the complexity of the fused ring system increases. Similar results are found with heterocyclic compounds. The spectrum has been used to examine the position of attachment of a sugar residue to a purine skeleton in some nucleosides[37], and spectral comparison with *N*-acyl indoles was important in fixing the structure of strychnine[38]. The pyrrole pigments have also been much studied, with special reference to chlorophyll and haemin[39]. The detection[40] of the 5,6-dimethyl-benziminazole skeleton by

its ultra-violet absorption was important in the early work on vitamin B_{12}; and the presence of the 1,4-naphthoquinone structure was detected[41] in the vitamins K by this means. In establishing the structure of terramycin, spectral differences between 5-hydroxy- and 7-hydroxy-indanones were used to fix the position of the hydroxyl group[42].

Some correlations between ultra-violet spectral features and stereochemical factors have been found. For example, in the polyenes, and in acyclic or monocyclic dienes, *cis* or *trans* structures have different spectral characteristics[43], although the details are rather complex. In simple α-substituted cyclohexanones, the absorption maximum of the carbonyl group is shifted slightly to shorter or longer wavelength, depending on whether the substituent is equatorial or axial[44]. It is possible that other methods described below provide more satisfactory criteria in these cases.

Quantitative determination of many natural products by ultra-violet absorption is now a standard procedure[45]. It has been invaluable with some of the vitamins, sterols and chlorophylls, and recently for the determination of sugars and amino-acids after interaction or co-ordination with reagents so as to bring the absorption band into a convenient spectral region.

INFRA-RED ABSORPTION

The infra-red absorption spectrum of a complex molecule can be used: (1) to discover the presence of particular groups, in the earlier stages of enquiry; (2) to discriminate between the alternative overall structures which have been suggested by detailed chemical work, even between different stereochemical forms; (3) to establish the identity of two specimens; and (4) for quantitative determination. Of these uses, the first two depend upon the principle that some of the nuclear skeletal vibrations can be localized within a bond or small group of atoms, the oscillation taking place almost independently of the remainder of the nuclear skeleton. This can only be an approximation, but it is sufficiently satisfied in the case of X—H vibrations, or those of multiple bonds such as C=O, C≡N, P=O, or in certain other deformations of X—H bonds. There must be no "mass" effects or coupling between vibrations of different parts of the skeleton, nor complications from Fermi resonance. Characteristic absorption bands may then be found, usually in the region 200–3500 cm^{-1} (2·8–50 μ).

Proof of identity is based on the fact that any complex molecule gives rise to a vibrational array and spectral pattern which is characteristic for the whole nuclear skeleton. This pattern involves both the positions and the relative intensities of absorption bands, and forms a "fingerprint" of the molecule. While a pair of optical enantiomorphs show identical spectra, all other structures should give different spectra; this often applies to stereoisomers which are closely similar, even with the same configuration but different conformations[46]. In solution, if interactions between dextro-rotatary and laevo-rotatary forms do not occur, a racemate should have the same spectrum as either enantiomorph, and this may avoid the need for optical resolution when only proof of identity is required.

Frequency correlation charts are, of course, well-known[47]. They should, however, be used cautiously, for unexpected shifts of band frequency or changes of band intensity often arise. To a spectroscopist, the dogmatic

VOL 2 1961

assurance shown by some organic chemists in the interpretation of the spectra is sometimes surprising. Care is also needed in making comparisons of spectra measured in different states of aggregation, or in different solvents, where one or another form of interaction may occur. Indeed, solvent effects may even prove useful in some specific cases for confirmatory diagnosis. Unfortunately, all this work must at present remain empirical, for we cannot yet calculate and predict exactly either the molecular vibration frequencies or the band intensities. This difficulty arises from insufficient knowledge of the internal molecular free field rather than from the complexity of the mathematical problem itself.

In recent years there have been a number of advances on the experimental side. Commercial recording spectrometers have been developed with better resolving power and speed, using prisms or gratings, not only for the conventional region 2·5–15 μ, but also for longer wavelengths to 40 μ and for the region 1–3 μ in which overtone bands are sometimes useful[48]. Where appropriate, the new fast detectors such as photoconductive cells have been introduced, and for much routine organic chemistry cheaper instruments of high quality have proved invaluable. The pressed disc technique (in which solid samples are embedded in an alkali halide matrix) has been developed, but great care must be exercised in using it owing to the effects of absorbed water vapour, of grinding and other factors which are not yet fully understood. It has proved useful, combined with the freeze-drying technique, in the study of lipids[49]. Cavity-type absorption cells (in which the sample is introduced into a hole drilled within a rock-salt crystal) have made it possible to use very small quantities of material, and such cells are being adapted to take off successive fractions from a chromatographic column. The reflecting microscope[50] has also been more widely used, with samples of 10 μg. Some of the difficulties of measuring infra-red spectra in aqueous solutions have also been overcome, and interesting results have been obtained with nucleoproteins, nucleic acids, polypeptides, amino-acids and carbohydrates, studied in both water and deuterium oxide[51]. The intense absorption bands of water lie at 3500, 1650 and 800 cm^{-1} but by the use of very thin layers between plates of such materials as calcium fluoride and silver chloride, and double beam compensation methods, the spectral features of the solute can be pieced together. In some cases, variations with pH or temperature have been found. One difficulty of using deuterium oxide as a solvent is the possibility of exchange with hydrogen in the solute. In other cases, such deuterium exchange has been used deliberately to help in sorting out complex spectral features and vibrational band assignments. Differential spectroscopy, by which parts of a complex spectrum can be cancelled out, leaving the features of less dominant components clearer for examination, has been applied successfully in the study of some natural oils.

In structural studies of natural products by means of infra-red absorption spectra the groups most commonly sought are OH, NH, CH_3, CH_2, CH, C=O and C=C, present in saturated or unsaturated systems, in open conjugated chains, or in rings of varying size and type. While a strong band at 3300–700 cm^{-1} usually provides confirmatory evidence for an OH or NH group, ambiguity can arise as a result either of hydrogen bonding or of

differences in the residue to which the OH or NH group is attached. The stretching vibration bands of C—H bonds between 2800–3300 cm^{-1} can to some extent be used to distinguish between saturated, olefinic and acetylenic types, and the higher frequency in a strained cyclopropane ring has been particularly useful (*Figure 1*). In all these cases, however, it seems that

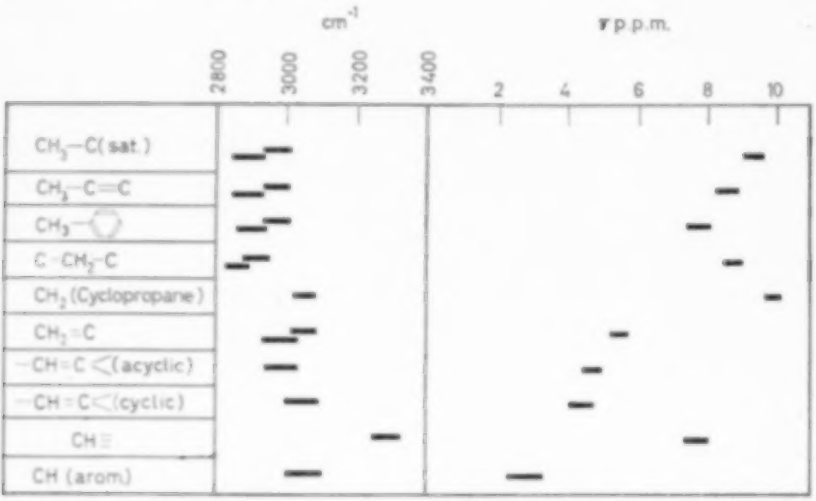


Figure 1. Characteristic C—H vibration frequencies and corresponding proton resonance shifts

greater discrimination can be achieved by using the chemical shift effect in the nuclear magnetic resonance spectra which will be discussed below. This chemical shift effect not only serves to distinguish types of OH, NH and CH groups in most cases, but is also able to reveal details of, for example, the skeleton to which a CH_3 group is attached.

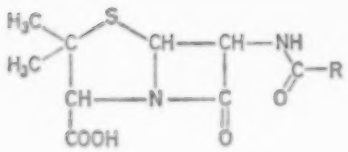
It is sometimes possible to resolve ambiguities in interpreting the C—H stretching vibration bands by taking into account also the bands due to deformation vibrations at longer wavelengths. These bands are sometimes significantly displaced by the contiguity of electronegative atoms or other inductive influences, but here again the more recent nuclear resonance spectra may prove more convincing.

The stretching vibration of the C=O group has been exhaustively studied, and its absorption band shifts considerably in different classes of compound[52]. This has been much used to decide between possible alternatives suggested by chemical work. For example, ultra-violet irradiation of verbonone (VIII) leads to the isomeric ketone chrysanthenone (IX); the very high C=O frequency of this (1785 cm^{-1}) indicates a strained cyclobutanone ring, and other spectral features (frequencies of 3030 and 1660 cm^{-1} are associated with =CH and $R_1R_2C{=}CHR_3$ groupings respectively) support the structure shown[53]. In the early studies on penicillin, much work centred on the C=O absorption bands 1600–1800 cm^{-1} which might have been attributable to an amide, fused β-lactam (X) or oxazolone (XI). Detailed studies on many amides and oxazolones were rather indecisive, but

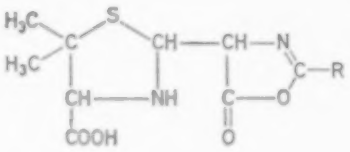
VOL. 2 1961

examination of some model fused β-lactams led Shell laboratories, Emeryville, to be the first to support the lactam–amide formula (X) which was subsequently confirmed by X-ray analysis[54].

(VIII) (IX)



(X)



(XI)

Among many other recent uses of C=O bands are the differentiation of γ- and δ-aldonolactones[55], determination of the structure of ketoflavones[56], studies on ketolactone oxidation products of camphor[57], and the analysis of tissue and serum lipids[58]. Sphingolipids show bands of an amide group at 1655 and 1550 cm^{-1} which are absent with all other lipids. Cephalin and lecithin have an ester group band at 1740 cm^{-1}, and can themselves be distinguished by other bands in the region of 1000 cm^{-1}. All these bands can be used for quantitative analysis.

The spectral characteristics of C=C and C≡C bonds, alone, conjugated or cumulated, are also useful. For example, they provide convincing support for the structure of mycomycin (XII)[59] (*Table 1*). The characteristic

$$H{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}COOR$$

(XII)

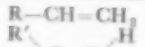
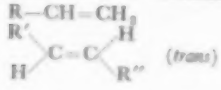
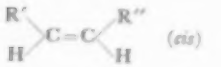
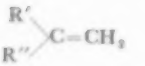
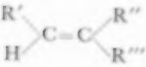
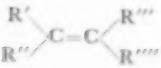
vibration of the C≡N near 2250 cm^{-1} was used[60] to detect this group in vitamin B_{12}.

Table 1. Spectral properties of mycomycin

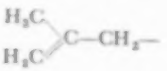
Grouping	*Spectral characteristics*
—C≡CH	3280, 2040 cm^{-1}
R′—C≡C—R″	2200 cm^{-1}
—CH=C=CH—	1930 cm^{-1}
—C≡C—C≡C—	U.V. 2560, 2670, 2810 Å
—COOR	1733 cm^{-1}

Another important set of bands is provided by the substituted olefins[61]. These occur in the region of 10 μ and are associated with bending motions of olefinic C—H bonds (*Table 2*). Either alone, or taken together with the

Table 2. Frequencies of characteristic bands in the infra-red absorption spectrum of olefins, associated with C—H deformation (δ_{C-H}) and C=C stretching (ν_{C-C})

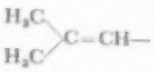
Olefins	δ_{C-H} (cm^{-1})	ν_{C-C} (cm^{-1})
	905–915; 985–995	1635–1650
 (*trans*)	960–970	1665–1675
 (*cis*)	~690	1650–1660
	885–895	1645–1655
	790–840	1665–1675
	–	1665–1675

C=C stretching vibration bands, these bands have been widely used in studying complex molecules, for they appear to apply reliably whether the unsaturated group is in a side-chain or in a ring. In this way, the isopropenyl (XIII) or isopropylidene (XIV) end groups of simple terpenes



(XIII)

(Band frequencies: 890 and 1645 cm^{-1})

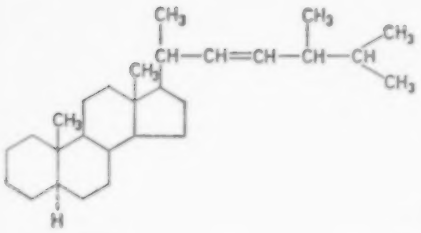


(XIV)

(Band frequencies: 810 and 1670 cm^{-1})

were investigated[62]. The *cis* or *trans* structure of the —CH=CH— group has been examined in many cases. Thus the double bond in the side-chain of Δ^{22}-ergostene (XV)[63] is shown to be *trans* by the band at 970 cm^{-1}. The corresponding bonds in calciferol (XVI), in tachysterol, and in the precursor of calciferol have also been examined in the same way[64]. The absence of the band at 965 cm^{-1} indicates a *cis* structure for jasmone (XVII) and cinerolone[65], and a band at 899 cm^{-1} has been assigned to a terminal methylene group in nyctanthic acid[66] (XVIII) a seed extract related to the tetracyclic terpenes. The same characteristics have been used in attempts to determine the *cis–trans* relationships in α,ω-diphenyl polyenes (XIX) and in β-carotene (XX)[67]. With simple *cis* or *trans* fatty acids and lipids this differentiation is straightforward.

VOL. 2 1961



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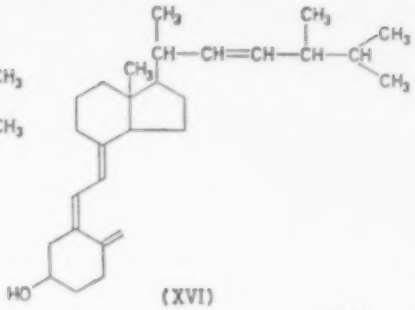

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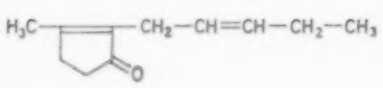

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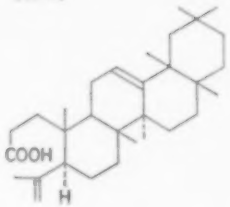

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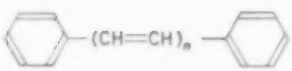

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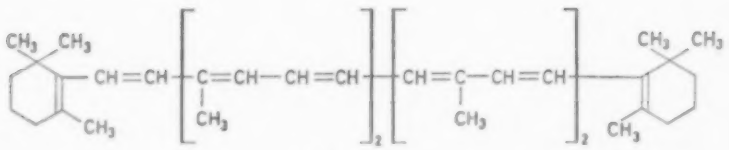


(XX)

Many of these simple correlations have been used, together with ultra-violet and nuclear resonance data, in establishing the structures of the interesting new plant growth promoting factor, giberellic acid, and the associated giberellins[68], and, together with other characteristic vibration frequencies of linkages involving nitrogen atoms, in fixing the structure of highly complex alkaloids such as lycoctanine and its derivatives[69].

Some intense infra-red bands in the region 11–15 μ occur with substituted aromatic rings[70]. These are associated with out-of-plane bending motions of the residual C—H bonds, and sometimes provide immediate evidence about the positions of the substituents. Moreover, the rules often appear to apply for fused aromatic ring systems[71]. The approximate frequencies of these bands are given in *Table 3.* However, these bands are somewhat unsatisfactory criteria for the presence of substituted aromatic rings, not only because of the rather wide frequency variation in some cases, but also since their intensity varies in an unpredictable way as the nature of the substituents is changed. A more reliable indication is the general pattern of bands between 1600–2000 cm^{-1} arising from combinations of the out-of-plane skeletal vibrations[72] (see *Figure 2*).

Table 3. Characteristic bands in the infra-red absorption spectrum of aromatic rings, associated with C—H deformations

Grouping	*Frequency* (cm^{-1})	*Grouping*	*Frequency* (cm^{-1})
Benzene	671	1,2,4-Trisubstituted	815 ± 10; 875 ± 5
Monosubstituted	750 ± 20; 700 ± 10	1,3,5-Trisubstituted	835 ± 25; 700 ± 25
1,2-Disubstituted	750 ± 15	1,2,3,4-Tetrasubstituted	805 ± 5
1,3-Disubstituted	780 ± 30; 700 ± 10	1,2,3,5-Tetrasubstituted	845 ± 5
1,4-Disubstituted	820 ± 10	1,2,4,5-Tetrasubstituted	860 ± 10
1,2,3-Trisubstituted	770 ± 10; 725 ± 20	Pentasubstituted	870

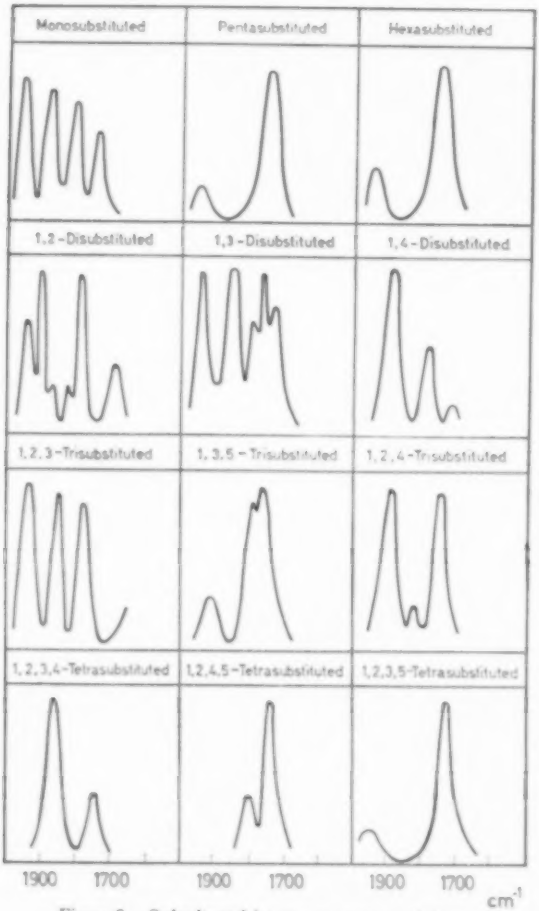


Figure 2. Substituted benzenes, pattern 5–6 μ

The class of natural products in which infra-red absorption has been most studied is the steroids[73]. Different side-chains attached at the C–17 position in this perhydrocyclopentenophenanthrene system give rise to the pregnanes, bile acids, cholestanes and ergostanes. With all these

VOL. 2 1961

compounds, information can be obtained about the structure and conformation of the nuclear skeleton, and about the side-chains. In saturated systems, C=O groups in rings A,B,C or at C–20 in the side-chain have about the same vibration frequency, but in the five-membered D ring the value is noticeably higher. Conjugated unsaturation in all cases lowers the carbonyl group frequency significantly. In side-chain ester groups, this frequency is higher than that in the ketones, and may coincide with that in the D ring, but the latter also has a band in the region 1100–1200 cm^{-1}. Some bands of the ring CH_2 groups are affected in definite ways by adjacent carbonyl groups. Many other correlations, including some for the steroid lactones, have been worked out[74], and more complex polycyclic terpenes are now being examined in the same way.

The relation between the infra-red absorption spectrum and stereochemical factors is particularly interesting. First, closely related diastereoisomers have different spectra, although these are complex. Thus cholestane and coprostane, differing only in the *trans* or *cis* arrangement at the fusion of rings A and B, have different spectra[46]. Also, spectral differences have been established empirically between compounds containing a substituent group in the axial or equatorial position.

Thus the acetate band at 1240 cm^{-1} in 3-acetoxy- steroids is single if the group is equatorial, but split into several peaks if it is axial[75]. Axial OH groups in the 3-position usually give a band near 1000 cm^{-1} (probably determined by the C—O band vibration), but this lies higher at 1040 cm^{-1} if the group is equatorial. This variation of frequency can be interpreted in terms of the likely effect of motions involving a greater or less amount of bond stretching or bending. The rules are not without exceptions, but have been applied to establish the axial orientation of the OH group in luminestan-3β-ol[76].

Similar correlations between conformation and spectrum have been found with the decalols[77], and in deuterium-substituted steroids the C—D bond frequency varies for axial and equatorial positions[78]. Also, when a halogen atom is introduced in an equatorial position on the carbon atom next to a carbonyl group, the carbonyl group band shifts to higher frequency, whereas no such effect occurs when the group is axial[79]. This result is paralleled by data on the ultra-violet absorption spectra referred to above. Similar conformation effects have been examined for the OH groups in carbohydrates[80].

Reference has been made already to infra-red work on lipids, and there are many applications in biochemistry[81]. Amino-acids, polypeptides and proteins have been much studied, and important spectral differences have been found between the open and closed chain forms of polypeptides[82]. Measurements with polarized radiation on crystalline materials or oriented fibres can provide information about the relative orientation of N—H and C=O bonds and about the type of hydrogen bonding involved. There is a serious difficulty of principle here, since the directions of dipole vector change during a vibration may not coincide exactly with a preconceived bond direction, but even semi-quantitative measurements from the band intensities with polarized radiation are valuable. Deoxyribonucleic acid can be distinguished from ribonucleic acid by its band at 1020 cm^{-1}, and

its spectrum is consistent with the structure derived from X-ray work[83]. Preliminary studies of bacteria and viruses show differences in composition which are worth further examination[84].

Many ambiguities arise in the application of the vibration frequency correlation rules. Attempts have been made to remove some of them by using the intrinsic intensities of the absorption bands[85]. In some cases this may be possible. For example, the intensity of the stretching vibration band of the N—H group in different classes of compounds varies considerably[86]. In aliphatic secondary amines it is low, but in heterocyclic bases, such as carbazole, it is high. In fact, the very low intensity of this group in certain alkaloids has caused anxiety. If the first overtone bands are also studied, an even better differentiation of the NH types is obtained. Similarly, there appears to be a significant difference in the O—H band intensity in phenols on the one hand and in alcohols on the other[87], and regularities occur in the intensities of different kinds of C—H bands[88]. With steroids, intensities can also be used to discriminate between carbonyl groups in different ring positions and in the side-chain[89]. An interesting example has been found with cisoid and transoid α,β-unsaturated ketones[90]. With cisoid types, the intensities of C=C and C=O bands are about equal, but with transoid types the C=O band is relatively much stronger. Although the attached groups give rise to minor variations, the rule seems to be reliable enough to apply in complex compounds. For instance, cholestan-5-en-4-one (cisoid) can be distinguished from cholestan-4-en-3-one (transoid) in this way.

However, accumulating evidence suggests that, in general, the band intensities (which are, of course, determined by different factors from those which control the vibration frequencies) are very susceptible to electronic effects of neighbouring atoms and groups, so much indeed as to limit their present value. A more detailed examination of these electronic influences is being carried out in the hope that the variations can be predicted or at any rate reconciled with structural details[91].

NUCLEAR MAGNETIC RESONANCE

Nuclear magnetic resonance spectroscopy is, perhaps, the most important new method for investigating details of molecular structure. It makes use of the magnetic effect set up by a spinning charged nucleus to get information about the chemical environment in which the particular nucleus occurs. Nuclei of even atomic mass and even atomic number, such as ^{12}C, ^{16}O and ^{32}S, do not spin, and this is indeed fortunate as far as applications to organic chemistry are concerned, since otherwise the nuclear resonance spectrum arising from a carbon chain might be too complex for general use. Nuclei such as ^{1}H, ^{19}F, ^{13}C, ^{15}N and ^{31}P have a spin moment $I = 1/2$, and we are primarily concerned with these. With other spinning nuclei, such as ^{2}H, ^{14}N, ^{17}O and ^{35}Cl, complications arise, partly as a result of the effects of their quadrupole moments.

A nucleus of spin angular momentum I gives rise to an equivalent magnetic moment μ which can be oriented in $(2I + 1)$ directions if placed in a homogeneous magnetic field H. The energy difference between two such adjacent levels is given by the relation

VOL. 2 1961

$$h\nu = \frac{\mu H}{I}$$

In a proton (^{1}H) with a spin $I = 1/2$, only two orientations are possible, and the small difference in energy level associated with each of them leads to a slight difference in population of the levels in accordance with the Boltzmann factor. In a given field strength H, therefore, there is a particular resonant frequency corresponding to the quantum of energy which is required to tip the nucleus from one orientation to the other. Alternatively, for a given supplied frequency, there will be a specific field strength corresponding to the resonant condition. It is usual, for experimental convenience, to maintain a constant frequency and vary the applied field strength.

Several factors can lead to broadening of the absorption line, especially with solids, but in liquids and gases these are minimized as a result of molecular motions, and sharp resonance lines arise.

The use of this phenomenon in molecular structural determination is based upon two additional effects. First, the electronic space clouds surrounding a spinning nucleus exert a screening effect which makes the effective magnetic field strength different from that applied.

$$H = H_{\text{appl.}}\,(1 - \sigma)$$

A slightly different field strength from that relating to a "free" nucleus must, therefore, be applied to obtain resonance at a fixed absorbed frequency. The extent of the so-called chemical shift varies with the particular skeletal environment, and can be correlated with the ionic character of particular bonds, with the inductive and mesomeric effect of substituents, and with the magnetic anisotropy of the molecule concerned.

In practice, it is not possible to measure absolute values of field strength with the same accuracy as it is to determine differences of field strength. Chemical shifts are, therefore, measured with reference to standard reference lines, such as are provided by water, cyclohexane, benzene or tetramethylsilane. Also, since the chemical shift is proportional to the field strength, it is desirable to represent it as the dimensionless unit

$$\delta = \frac{H_{\text{subst.}} - H_{\text{ref.}}}{H_{\text{ref.}}} = \sigma_{\text{subst.}} - \sigma_{\text{ref.}}$$

It can also be expressed as

$$\delta = \frac{\Delta}{\text{oscillator frequency}} \times 10^6$$

in which Δ is the frequency shift between sample and reference corresponding to the change in field strength, δ then being expressed in parts per million. In different nuclei, δ may vary between a few parts per million (as with protons) and a few per cent (as with cobalt). Recently, another quantity

τ ($= 10 - \delta$) has been suggested for use with the proton taking tetramethylsilane as the reference substance, so that a set of simple numbers are obtained for the shifts of all except the most acidic protons.

A difficulty arises here, however, which has led to some confusion in the correlation of many results so far obtained. If the reference substance is used internally, mixed with the sample, there must be no interactions. If it is used externally, in a separate probe, corrections must be applied to allow for differences in the bulk susceptibilities of the two samples. Unfortunately, both external and internal standards have been used in the past, as well as different reference substances, and it is not always possible to correct different recorded data so as to use them together in making comparisons of chemical shifts. In the illustrative examples, which follow, various scales of reference will be used.

The second effect which is important with organic molecules arises from a spin–spin interaction between neighbouring nuclei. As a result of this, the resonant line for a proton may be split by the magnetic disturbance of the other neighbouring protons into a pattern which is highly characteristic, and which makes it possible to designate the nature of the adjacent atomic groupings. This effect, which is independent of the applied magnetic field, is transmitted through the electron space cloud of the molecule and diminishes rapidly as the distance between the interacting nuclei is increased.

A point of particular importance is that the integrated intensity of a nuclear resonance absorption line is a direct measure of the number of nuclei of the type concerned. If the relative intensities of lines at different resonant frequencies are compared, such as those which arise with protons subject to different chemical shifts, it is at once possible to count the number of groups of different kinds, and this is strikingly useful in solving certain structures. Certainly here the method has considerable advantages over the use of the infra-red absorption spectrum.

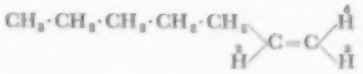
The design of equipment for these measurements is partly determined by whether low or high resolution is required[32]. It is essential, however, to have a high degree of magnetic stability and homogeneity. Permanent magnets, thermostatically controlled, have stability, but electromagnets can have higher field strength, and may be required for less sensitive heavier nuclei. Greater field homogeneity over the required area can be obtained with correcting coils on the pole pieces, and it is usual to spin the sample to obtain an even greater effective field homogeneity. The sweep rate used in searching for the signal must be carefully controlled in relation to the relaxation time in the sample.

Usually 0·5 cm^3 of liquid sample is adequate, but much smaller quantities have sometimes been used. For proton resonance, suitable solvents are carbon tetrachloride, tetrachloroethylene, carbon disulphide, deuterochloroform, trifluoroacetic acid, dimethyl sulphoxide, trichloroacetonitrile, dimethyl formamide, water, cyclohexane, benezene, dioxane and acetone. Many of these have been used to give an internal reference signal, although cyclohexane and tetramethylsilane are now regarded as the most suitable. A change of solvent sometimes causes shifts which are useful in splitting up overlapping lines. The limited solubility of some compounds introduces a difficulty, since, in order to obtain a satisfactory signal strength, larger

VOL. 2 1961

samples or a higher field strength will be required, and both are undesirable in the interest of a uniform and stable field.

As already explained, the proton resonance signals in C—H bonds of saturated, unsaturated or aromatic hydrocarbons give very characteristic chemical shifts. In hept-1-ene (XXI), or in *cis*-propenylbenzene (XXII), for example, each type of proton gives a distinct signal[93] (see *Table 4*).



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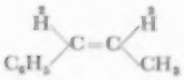


(XXII)

Table 4. Characteristic chemical shifts of proton magnetic resonance signals in C—H bonds

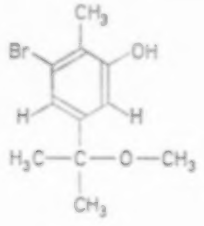
		δ (ref. H_2O)
Hept-1-ene (XXI):	$\overset{5}{H}$	−1·1
	$\overset{3}{H}$	−0·4
	$\overset{4}{H}$	−0·2
	CH_2—C=C	+2·8
	CH_2 (sat.)	+3·5
	CH_3	+4·0
cis-Propenylbenzene:	$\overset{2}{H}$	−1·2
	$\overset{3}{H}$	−0·5
	CH (arom.)	−2·0
	CH_3	+3·5

Similarly in ethylphenylacetate, distinct signals are obtained for the CH_3, CH_2, CH_2CO and C_6H_5 protons, split in some cases by spin interactions[94].

In substituted benzene rings, the aromatic proton shifts differ according to the relative position and nature of substituents, and in polynuclear fused aromatic hydrocarbons or in azulenes the protons in different locations can be distinguished. The same applies to protons in heterocyclic rings such as furans, pyridines and thiophenes, and the chemical shifts are in some cases made more distinctive by spin interactions. The differences in pattern between glyoxalines and pyrazoles was used recently to confirm the presence of a pyrazole ring in an amino-acid extracted from water-melon seed[95]. The presence of a 2,3-disubstituted pyridine ring in a new alkaloid has also been established in this way[96], and of a 1,4-dihydropyridine skeleton in a phosphopyridine nucleotide[97].

With protons attached to elements other than carbon, or with CH_3 or CH_2 groups attached to different kinds of group, the chemical shifts vary over a wide range[98]. Many of the earlier data require revision or correction, but it is certain that striking differences occur between groups which are often difficult to distinguish or established by other methods. For example, unless hydrogen bonding complicates the situation too much, it is possible to distinguish between the OH groups in alcohols and phenols, the SH groups in mercaptans or thiophenols, or the NH groups in different types of amine. Infra-red methods are not always conclusive in these instances.

The relative intensities of the signals often provide additional evidence. For example, a cresol derivative[99] was shown to possess structure (XXIII) since, apart from the phenolic and ring protons, it gave three CH_3 resonances of relative intensities 3:3:6. The alternative structure (XXIV) would have given five such resonances of intensities 1:2:3:3:3.



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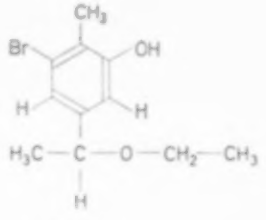

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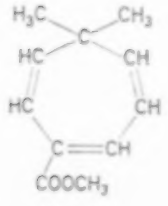

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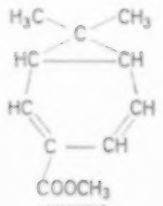


(XXVI)

Thujic acid methyl ester provides a similar example[100]. This compound gave three resonances of relative intensities 5:3:6 (due to $=CH$, $COOCH_3$ and $C(CH_3)_2$ respectively), thus confirming structure (XXV) rather than (XXVI), since the latter would have given four resonances of relative intensities 3:2:3:6 (due to $=CH$, CH, $COOCH_3$ and $C(CH_3)_2$ respectively). The spin–spin patterns are often complex, and can be much affected by the relative values of the chemical shifts of the groups between which spin interactions are occurring. The principles, however, can be illustrated by some simple cases. For example, in the molecule HD, with the spins of proton and deuteron 1/2 and 1 unit respectively, the proton can, so to speak, " see " three orientations of the deuteron $(+1, 0, -1)$ and the proton signal is a triplet. The deuteron " sees " two orientations of the proton $(+1/2, -1/2)$ and its signal is a doublet. In $^{31}P\ ^{19}F_3$, the fluorine nucleus

" sees " two orientations of the phosphorus nucleus ($+ 1/2$, $- 1/2$) giving a doublet, whereas the phosphorus nucleus " sees " four combinations of the fluorine species ($+ 3/2$, $+ 1/2$, $- 1/2$, $- 3/2$), of which two have three times the statistical weight of the other pair, the P resonance therefore being a quartet, 1:3:3:1.

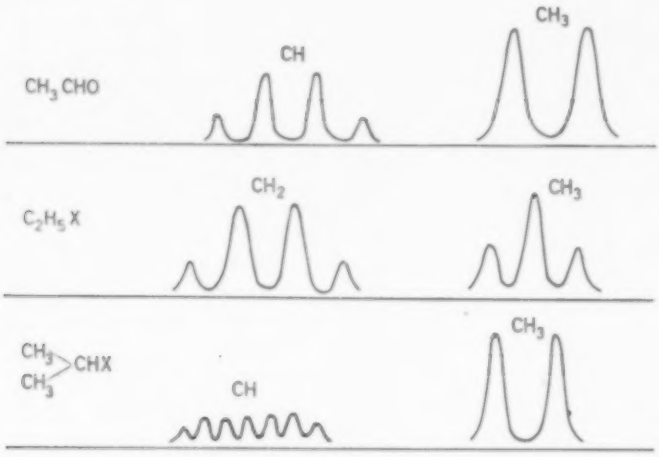
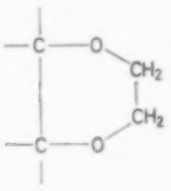


Figure 3. Spin-spin multiplets of proton resonance

In ethyl alcohol or diethyl ether, the CH_3 and CH_2 groups of the ethyl radical split into three and four components, with relative intensities corresponding to the statistical weights of the levels (see *Figure 3*). n-Propyl and isopropyl groups attached to a residue X can be distinguished. In the simplest case, the iso-propyl group will give two lines for the CH_3 groups which " see " two orientations of the adjacent proton, and the CH group will have seven lines due to the sets of orientations of the six protons in the methyl groups ($+ 3$, $+ 2$, $+ 1$, 0, $- 1$, $- 2$, $- 3$), as shown in *Figure 3*. In the n-propyl group of $CH_3 \cdot CH_2 \cdot CH_2 \cdot X$, the methyl group will give a triplet, the α-methylene group a triplet, and the β-methylene group a set of twelve lines. Chemical shifts determined by X may complicate the general appearance, however, and complete resolution of the multiplets is not always obtained. In $CH_3 \cdot CHO$, a quartet and doublet are found associated respectively with the CHO and CH_3 groups (see *Figure 3*). The $—CH_2—CH_2—$ or $—CH_2—CH_3$ groups in ring ethers of the type (XXVII) or (XXVIII) can be distinguished; the $\geqslant CH—CH_3$ group gives a quartet (CH, 1:3:3:1) and doublet (CH_3, 1:1), but the $—CH_2CH_2—$ group only



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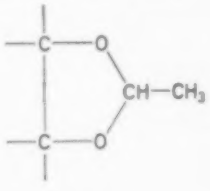
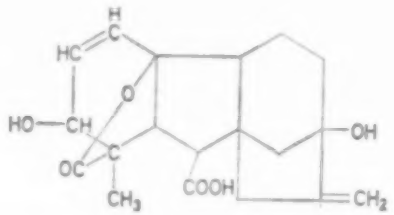


(XXVIII)

a single line which may be split to a greater or less extent as the general symmetry of the attached residue is disturbed.

These principles have been applied in structural determinations of many natural products. Evidence for the group $\geqslant C-\underset{\underset{O-}{|}}{CH}-CH=CH-$ has been important in fixing the structure of giberellic acid[101] (XXIX). The characteristic chemical shifts of protons in the groups $CH_2=C<$ and $\geqslant CH$ found with Feist's acid, and the absence of CH_3 resonances at high field, show[102] that this substance contains a saturated cyclopropane ring with an exocyclic methylene group, and possesses structure (XXX) rather



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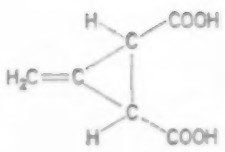

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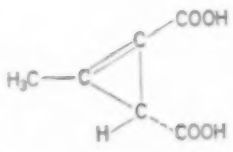


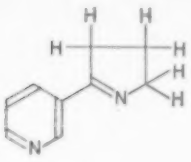
(XXXI)

than (XXXI). This is confirmed by the intensity distribution, formula (XXX) giving three lines of equal intensity, and (XXXI) three lines of relative intensity 2:1:3.

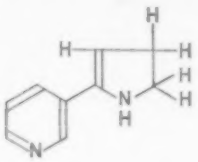
Among alkaloids which have been studied, myosmine has a set of four nuclear resonance lines of equal intensity due to the four different pyridine protons, with three other lines at higher field, each of which has twice the intensity of the pyridine protons[103]. This fixes the structure as (XXXII) rather than (XXXIII). The side-chain group $-CH(CH_3)_2$ and the position of the methoxy-group have been determined in lunacrine (XXXIV)[104], and the $N-CH_3$ group has been detected in aspidospermine[105].

Much useful information has been obtained from the proton resonance spectra of essential oils and glycerides, by using the characteristics of groups such as CH (aromatic), OH, CH_3CO, $-CH=$, CH_2 and CH_3 groups in different environments[106]. Sterculic acid was recently shown to contain a cyclopropene ring in the middle of a long fatty-acid chain[107].

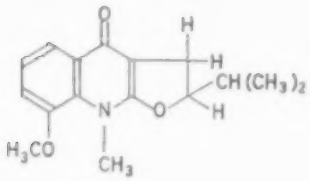
VOL 2 1961



(XXXII)



(XXXIII)



(XXXIV)

The nature of the end-groups in carotenoid-type molecules such as a spirilloxanthin and the paprika pigments have been determined[108]. The tentative structure originally proposed for spirilloxanthin was (XXXV), where R = R′= (a). However, the spectrum is only explained if the end groups are (b). In the paprika ketones[109], characteristics of CH_3 groups on saturated quaternary carbon atoms have led to a similar revision of ideas about the end groups. The stereochemistry of these conjugated chain systems has also been examined in relation to the nuclear resonance spectra by reference to simpler related molecules such as the dimethyl muconates.

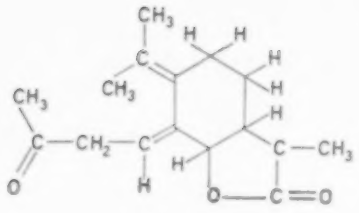
With methyl photosantonate (XXXVI)[110], the resonance signals due to $(CH_3)_2C=$ and $=CH—CH_2—COOCH_3$ proved invaluable in fixing the structure; and in ψ-santonin (XXXVII), a sesquiterpene lactone, one olefinic proton has been recognized among a large number of saturated group protons[111].

The chemical shifts of CH_3 groups in helvolic acid (XXXVIII) have led to the determination of the end-group in the side-chain, one such group being assigned to the C-24 position [34].

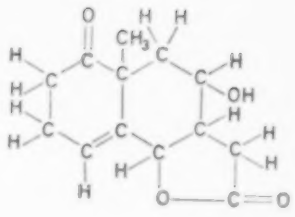
With steroids in general, characteristic resonances occur for CH_3 groups on quaternary carbon atoms, and for acetoxy-, olefinic CH=, and other groups in different locations in the skeleton[112]. These appear to offer great

(XXXV)

(a) (b)

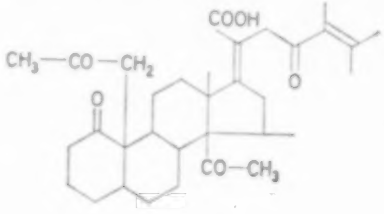


(XXXVI)



(XXXVII)

possibilities for structural determination. The chemical shifts are also affected by stereochemical conformation, so that axial and equatorial H atoms can be distinguished. Such conformational effects in the proton resonance spectra have also been found with acetylated pyranoses and inositols[113], and are confirmed by results on similar conformations in such compounds as trioxane[114], the *cis*- and *trans*-decalins[115], the dimethylcyclohexanes[116], and 2-acetoxy-1,3-dimethoxycyclohexanones[117].



(XXXVIII)

The use of spinning nuclei other than protons is still in its early stages of development, but this offers great possibilities, especially perhaps with ^{13}C, ^{19}F and ^{31}P which have a spin $I = 1/2$, and no quadrupole moment. The signal strengths are intrinsically weaker, so that larger samples are needed, as well as better detecting equipment. Also, owing to the greater relaxation times, the sweep rate has to be controlled carefully. However, the chemical shifts are much greater than those for protons, and they are very sensitive to structural changes. In ^{13}C, the chemical shifts referred to a benzene carbon nucleus as zero vary from about + 120 in hydrocarbons to − 80 in ketones[118]. The location of these ^{13}C resonances is far removed from that of protons, and the spin coupling with bonded hydrogen atoms leads to characteristic multiplets. With $CH_3 \cdot COOH$, using the natural abundance of ^{13}C, the carbon nucleus of the COOH group appears as a single resonance, and that of the CH_3 group as a quartet at higher fields. In dimethyl acetylene di-carboxylate there are resonances characteristic of the —CO—O—, —C≡C—, and —OCH_3 groups. In mesitylene, the chemical shifts of the 2, 4 and 6 carbon atoms are convincingly different from those of the non-equivalent 1, 3 and 5 carbon atoms.

Resonances of ^{31}P nuclei in different environments show even larger

VOL. 2 1961

chemical shifts[119]. The experimental difficulties are at present considerable, but it may be possible to discover by this means features of phosphoryl compounds. Indeed, all these results encourage the hope that, by a study of resonances of several nuclei such as ^{1}H, ^{13}C and ^{14}N in the same molecule, it may be possible to determine a sufficiently large number of structural units in that molecule to fix its whole structure without recourse to much chemical work on degradation or synthesis.

Other refinements in technique seem likely to remove some of the present difficulties. One is the double irradiation method[120]. When spin interactions lead to a highly complex spectrum, it may be possible to decouple these spins by irradiation with a field close to the resonant frequency of one of the nuclei, thus simplifying the spectrum and its use for diagnosis. Another way of enhancing chemical shifts in certain cases is by adding paramagnetic salts which co-ordinate with hydroxyl or other groups[121]. A still more interesting development is electronic-nuclear double resonance, in which the substance is irradiated with intense microwave radiation at a frequency which excites the electron resonance of any paramagnetic material present. Strong interactions may come into play which lead to a large increase in the intensity of the nuclear resonance absorption, and the effect may be useful in studying some of the heavier nuclei.

Electron paramagnetic resonance itself has been applied to the study of certain natural products[122]. These include, for example, the porphyrin types in which a paramagnetic ion is surrounded by an organic skeleton, as in haemoglobin, myoglobin, chlorophyll or the phthalocyanines. In this way, important information can be obtained about the symmetry of the central part of the structure and about the type of bonding to the central metallic atom.

OPTICAL ROTATORY DISPERSION

Optical rotation has long been used as a criterion for purity, proof of identity, for the determination of enantiomorphic type, and, to some extent, as an indication of the position of a functional group or of the relative configuration of different asymmetric centres in a molecule. Empirical rules have been proposed for computing the optical rotation of compounds within a class of compounds such as the steroids by addition of definite amounts for different structural units present in the molecular skeleton[123]. In this way, using rough measures for C=C, OH, CH_3CO and C=O groups at different positions, useful corroborative evidence about the structure of certain steroids was obtained.

Optical rotation is equivalent to circular birefringence, and occurs when a substance transmits the left- and right-hand components of a beam of circularly polarized light with unequal velocity. If these components are absorbed unequally, the optical rotation will vary with wavelength, and classical equations have been proposed to express this. Indeed, some workers have used the optical rotation at two wavelengths as a refinement for structural work and for a criterion of purity. The variation of specific rotation with wavelength becomes greater as the absorption band is approached, and, as it is traversed, a Cotton effect may be observed, the

optical rotation changing rapidly in magnitude and sign[124] (see *Figure 4*). This arises when the vibrating electric moment associated with the optical absorption band has non-parallel coplanar components in separate parts of the molecule. The anisotropy is high when the absorption coefficient is

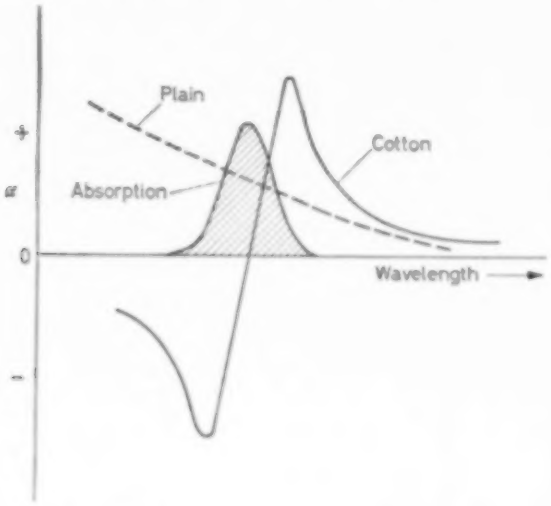


Figure 4. Optical rotatory dispersion

low, and this makes the phenomenon sensitive to structural changes which, in general, affect a weak absorption band more than a strong one. The variation of optical rotation with wavelength is described by a plain curve, a single Cotton curve or a multiple Cotton curve when several absorption bands are effective.

In recent years, above all from the work of Djerassi and his co-workers[125], it has become clear that the characteristics of these curves are remarkably sensitive to structural factors, such as the proximity of the absorbing group to any asymmetric centre or conformational differences.

The measurement of rotatory dispersion curves involves greater experimental difficulties than might be expected, and, at present, little work has been done outside the range 7000–2500 Å. Conventional prism spectrometers may be used, but, owing to absorption and energy loss in the polarizers, far greater sensitivity in detection is needed, and intense light sources have been used such as tungsten, zirconium or xenon arcs, with photoelectric recording. It is desirable to extend these measurements to shorter wavelengths, and also into the infra-red region[126]. Different polarizing equipment will be required, and there are still other problems if a robust sensitive instrument is to be developed which will record the optical rotation curves across a wide region continuously and directly.

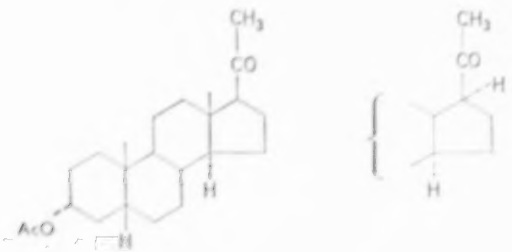
The choice of solvent may be determined by solubility considerations, but it must be transparent, and dioxan and methanol have been much used. It is important to note that a change of solvent may cause some fundamental

VOL. 2 1961

alterations, especially when the solute molecule is flexible and can exist in different solvents in different preferred conformations. The rotatory dispersion curves of 2-chloro-5-methylcyclohexanone are, for example, quite different in methanol and in octane solution[127].

Plain rotatory dispersion curves down to 2600 Å are found with compounds, such as amino-acids or carbohydrates, which have no chromophore absorbing at the longer wavelengths. Most work has been done with compounds containing a carbonyl group, since its intrinsic absorption coefficient is low, and the band lies in a convenient spectral region. In the aliphatic aldehydes, the size and shape of the Cotton effect curve depends on the length of chain, the curve approaching a plain curve as the separation of the asymmetric centre from the absorbing group is increased. Far more important work has been done with cyclic compounds, and two general principles can be laid down: (1) that enantiomorphs give mirror-image Cotton effects; and (2) that similar stereochemical environments in the region of the carbonyl group lead to similar dispersion curves.

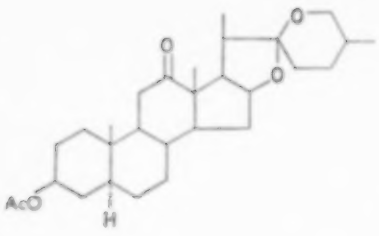
The rise in absolute value of the optical rotation near the absorption band provides a new, more sensitive, method of quantitative analysis. For example, the pair of isomeric C–17 ketones (XXXIX), pregnane-3α-ol-20-one acetates, have Cotton effects of different sign, and at 3075 Å their specific rotation differs by 3600°. A mixture can therefore be analysed easily[128].



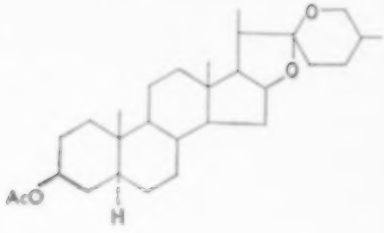
(XXXIX)

Another simple case arises when one component contains an absorbing chromophore leading to a large Cotton effect, while the second component has no such group and gives a plain curve. This occurs with hecogenin (XL) and tigogenin acetates (XLI)[129], a pair of saponins involved in the manufacture of cortisone. In some respects this method of detecting trace impurities is more sensitive than the infra-red absorption spectrum, but it suffers from the disadvantage that the Cotton curves in themselves give no direct indication of the nature of the impurities.

With ring ketones such as the steroids, factors which affect the optical rotatory dispersion (O.R.D.) curve are ring size, *cis* or *trans* fusion of rings, the relation of the carbonyl group to the ring junction, substituents at the junction or α- to the carbonyl group, and conformation of α-substituents or other conformational effects. The steroid skeleton contains many asymmetric centres, and the carbonyl group is always near to one of them.



(XL)

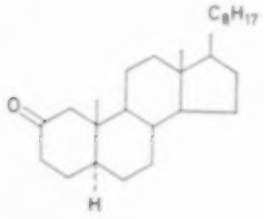


(XLI)

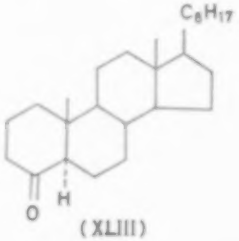
The results confirm many deductions from infra-red and ultra-violet absorption spectra, and from nuclear magnetic resonance, but sometimes reveal details unobtainable by other methods.

It is fortunate that, when a substituent is far removed from the carbonyl absorbing group, its nature has little effect upon the O.R.D. curve. Thus, in sapogenins, bile acids, and other classes with different groups at the C–17 position of the steroid skeleton, the rotatory dispersion characteristics of the main A/B rings remain the same.

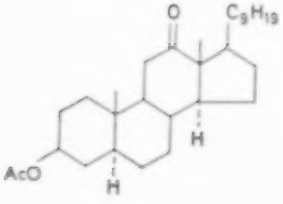
As already stated, the infra-red absorption spectra fail to determine the location of carbonyl groups in the A/B/C rings of steroids. The O.R.D. curves make this possible, and require only milligramme quantities of material. For example, the curves of cholestan-2-one (XLII) and -4-one



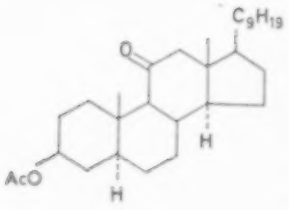
(XLII)



(XLIII)



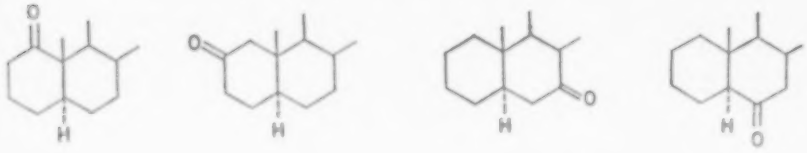
(XLIV)



(XLV)

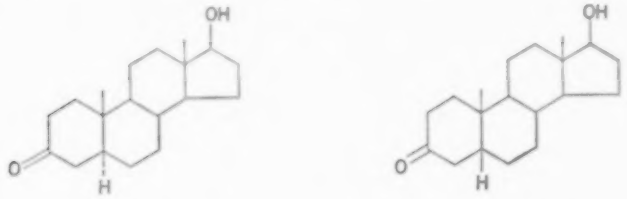
VOL. 2 1961

(XLIII) differ in sign[130]. A difference of amplitude is found with the acetates of ergostan-3β-ol-11-one (XLIV) and ergostan-3β-ol-12-one[131] (XLV). It seems also that, when more than one carbonyl group is present in a steroid, the O.R.D. curves may give information about them, whereas the infra-red absorption spectrum may be ambiguous. In the substituted decalones (XLVI), the O.R.D. curve is markedly dependent upon the location of the carbonyl group in relation to the substituents[132].



(XLVI)

Optical rotatory dispersion appears to be more specifically valuable in sorting out the stereochemical conformational problems of cyclic systems. For example, the 5α- and 5β- isomers, (XLVII) and (XLVIII), of androstan-17β-ol-3-one differ only in the A/B ring junction, but have quite different O.R.D. curves[133].



(XLVII) (XLVIII)

Very different O.R.D. curves also arise between cholestan-4-one and coprostan-4-one (5β cholestan-4-one)[128], and between cholestan-3β-ol-7-one acetate and 3α-hydroxy-7-ketocholanic acid, although, as already explained, changes in the C–17 substituent have no significant effect.

The O.R.D. curves for the *cis*- and *trans*-10-methyl-2-decalones, (XLIX) and (L), are opposite in sign[134], and correspond closely to those of 3-keto-5β- and 3-keto-5α-steroids respectively, again showing that the configuration around the absorbing carbonyl group is the dominant factor.

(XLIX) (L)

In the 5-hydroxy-10-methyl-$\Delta^{1(9)}$-2-octalones, the orientation of the C–10 substituent similarly determines the sign of the O.R.D. curve, and there is a correspondence with the curves of Δ^4-3-keto-steroids[135].

As already explained, spectral differences in both the infra-red and ultra-violet regions occur with keto-steroids according to the axial or equatorial positions of substituents. Similar effects are found with the rotatory dispersion curves. Axial and equatorial hydroxyl groups adjacent to the carbonyl group in steroids shift the mid-point of the Cotton curves to longer and shorter wavelengths respectively[136]. Acetoxy-groups have a similar effect, and, if axial, lead to enhanced amplitudes. The effect of α-halogen atoms is similar, and may even change the sign of the Cotton curve[137]. By consideration of these compounds, important rules have been formulated, and these bear upon the determination of absolute configurations and the semi-quantitative prediction of O.R.D. curves[138].

Many principles suggested empirically by these illustrations have been used to establish the stereochemistry of compounds such as lumisterol, luminsantonin and giberellic acid. Their extension to more complex systems such as the polycyclic terpenes is at present difficult, since the introduction of some substituents, *gem*-dialkyl groups, or extra fused rings often appears to affect the general conformation in unexpected ways. For example, the introdution of a pair of methyl groups at the C–4 position in cholestan-3-one has a remarkable effect, and the specific orientation of the isopropenyl group in α-cyperone (LI) leads to striking changes in the O.R.D. curve [139].

(LI)

In a random conformation such as exists in a strongly hydrogen-bonding solvent, polypeptides give plain O.R.D. curves. Only the α-helical forms give rise to a complex dispersion curve. The possibility of studying denaturation in this way has been examined, and this kind of work may be extended by using peptides containing an absorbing group such as a phenyl nucleus.

All these empirical data on optical rotatory dispersion should stimulate the development of a better theory of optical rotation in terms of the detailed electronic structure along the lines visualized by Moffitt.

Another related phenomenon, the Kerr effect[140] (the development of birefringence under a voltage gradient), promises to give structural information about molecular conformations and the axial or equatorial arrangement of substituents in saturated ring systems.

MASS SPECTROMETRY

The mass spectrometer has also been used for structural analysis. When molecules are subjected to electron bombardment, cleavage may occur and positive ions of both the original molecule and of its fragments may be formed. These ions can be passed through a mass spectrometer and their masses determined. The method has, of course, been used in recent years

VOL. 2 1961

for the analysis of hydrocarbon mixtures, since, with appropriate calibration, the measured intensities of the different fragment masses can be used to compute the composition of the original mixture. With complex molecules, this is being used to determine the molecular weights and also to estimate the mass numbers for side-chains or other main fragments of the molecular skeleton. The strength of the applied voltage determines the degree of fragmentation.

Steroids have been examined in this way. Cholestane[141], for example, of molecular weight 372, gives a set of fragments of molecular weight between about 40 and 360, which correspond to the residues expected. By this means, steroids and triterpenoids can be distinguished, and valuable clues obtained about side-chains. Recently, it has been applied to the study of new antibiotics such as lagosin[142] and filipin[143], and flavonoids[144], and seems likely to become more widely applied in preliminary studies on unknown structures which have molecular weights up to about 400.

OTHER PHYSICAL METHODS

Isotopes have been used in several ways in the study of natural products. As already explained, deuterium may be used in the interpretation of an infra-red absorption spectrum. This exchange process has also been applied, in conjunction with infra-red measurements, in work on large molecules such as cellulose or polypeptides; by this means it is possible on the one hand to discriminate between crystalline and amorphous parts of a complex structure, and on the other to differentiate between helical or open chain forms of the peptide chains[82].

^{14}C is now being widely used to elucidate the mechanism of biogenesis of many products, and has been invaluable in research on photosynthesis[145]. Irradiation of vitamin B_{12} and subsequent measurement of the radioactive decay gave a convincing confirmation of the presence of cobalt in this molecule. Tritium also has been used as a tracer in many synthetic reactions.

Reaction kinetic measurements themselves have provided evidence about certain structures and conformations. The electron microscope seems to be providing new information about the viruses.

For quantitative determination, reference has already been made to standard ultra-violet absorption methods for the assay of vitamins, porphyrins and other substances[146]. Polarography is sometimes convenient not only for estimating organic compounds but for identifying structures such as a conjugated system. Flame photometry or ultra-violet emission spectra with ashed products have been used for the determination of metals, but here the newer methods of X-ray fluorescence[147] or atomic absorption spectroscopy[148] offer great possibilities, and technical improvements are rapidly increasing their sensitivity.

The whole range of physical methods is indeed wide. Which method should be used in a given case will be determined by such considerations as the quantity of material available, its physical state and solubility, whether it is necessary to recover the sample or not, the particular question being asked, and whether it is required to predict the whole structure, or only part of it, or to confirm a structure already proposed.

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VOL
2
1961

APPLICATION OF OPTICAL ROTATORY DISPERSION STUDIES TO PROBLEMS IN NATURAL PRODUCTS CHEMISTRY. LV*

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Modern natural products chemistry—in terms of isolation, structure elucidation, determination of relative and absolute configuration, and finally chemical or biological synthesis—covers more facets of organic chemistry than any other single area of this science. The remarkable progress which has been achieved in this field during the past twenty years can be ascribed, to a considerable extent, to the eagerness with which the natural products chemist has been willing to employ techniques which were either developed for his specific purpose or, more frequently, discovered in another connection but clearly helpful to his own needs. For instance, at the isolation stage, one can hardly conceive of a natural products laboratory that does not employ elution, partition, paper or gas-phase chromatography. At the next step, structure elucidation, the organic chemist dealing with natural products has always been very receptive to the use of physical methods which would offer him, rapidly, preliminary information to delineate the more profitable areas of chemical attack. These physical methods were invariably discovered by physicists or physical chemists, but their extensive application to organic chemistry was usually accomplished by a semi-empirical approach in which a great number of organic compounds were examined, and then the chemical structure and the particular physical property under discussion were correlated. Chronologically, ultra-violet spectroscopy was followed by infra-red absorption measurements, then nuclear magnetic resonance studies and, about the same time, by the more extensive use of mass spectrometry.

In each case, the organic chemist, and especially the natural products investigator, accepted the particular physical method as soon as instrumentation became sufficiently advanced, so that these measurements could be conducted easily in or near his own laboratory. Furthermore, it should be noted that all of the above-mentioned physical measurements have invariably added information which was not available from the others, so that they have always tended to complement one another. We have, therefore, reached the point where most new natural products, after isolation, purification and elementary analysis, are subjected to a gamut of physical measurements before serious degradative efforts are initiated. Even during the

* For paper LIV, see C. Djerassi, *Endeavour*, **20**, 138 (1961).

degradative phase, which to many natural products chemists is intellectually the most stimulating and satisfying one, physical measurements of the type mentioned above play a crucial rôle.

All of these introductory statements apply to one of the newest physical methods introduced into organic chemistry, and especially into the chemistry of natural products, namely optical rotatory dispersion. In principle, it was known since the early part of the last century, yet its actual application by the organic chemist did not really commence until the nineteen-fifties, when the first readily operable (at least by the standards of the organic chemist!) spectropolarimeter became available. Once the utility of optical rotatory dispersion was demonstrated to the organic chemist, its use spread rapidly, and, barely five years after our first publications[1], this tool has become a routine adjunct to many aspects of natural products chemistry. Again, one of the principal reasons for its rapid acceptance was that optical rotatory dispersion offers information which is usually not available from other physical methods. Rotatory dispersion suffers from one limitation, which does not apply to ultra-violet and infra-red spectroscopy or nuclear magnetic resonance measurements, namely, the requirement that the substance be optically active. This is indeed a limitation in the broad area of organic chemistry, but it is practically negligible among natural products, since the vast majority of them is optically active. It is not surprising, therefore, that the major impetus to the modern development of optical rotatory dispersion came from a natural products laboratory.

VOL. 2 1961

As mentioned earlier, the phenomenon of optical rotatory dispersion—the variation of optical rotation with wavelength—has been known for a long time and studied extensively by theoretical and physical chemists. These classical studies have already been covered by Lowry[2] and subsequently by Levene and Rothen[3] and by Kuhn[4]; but they have hardly made an impact upon organic chemists, as witnessed by the fact that essentially no significant* rotatory dispersion measurements have been recorded in the literature between the nineteen-thirties and 1955. The recent and almost explosive developments in the field coincided with the appearance of the commercially available Rudolph spectropolarimeter[5], and they have been discussed in detail by the present author in a book[6] and also in a number of review articles[7, 8]. Except for a very short introductory section, recapitulating some principles of nomenclature and presentation of data[9], the remainder of this lecture will be concerned with direct applications to problems in the natural products field. During the past five years, optical rotatory dispersion has also played an important rôle in work on polypeptides and proteins[10, 11], but this special area will not be included as my research group has not contributed to it.

In principle, we can distinguish between two types of optical rotatory dispersion curves, examples of which are illustrated in *Figure 1*. A *plain curve* is one which does not exhibit a " maximum " (peak) or " minimum "

* By " significant " I am referring to dispersion measurements proceeding through the region of absorption of the particular chromophore under examination, rather than to a few rotation measurements carried out at several wavelengths outside the range of maximal absorption. Clearly, the latter will never result in the experimental determination of the Cotton effect, which forms the basis of most of the modern applications of rotatory dispersion in organic chemistry.

(trough), and is typical of substances which do not possess an optically active chromophore in the measured spectral range. Typical compounds exhibiting such curves are alcohols, acids and hydrocarbons, and the term " plain " is employed irrespective of whether the curve crosses the zero rotation axis (see *Figure 1* for plain negative curve starting on the positive side in the visible), or whether it always possesses the same sign. In contrast to the nomenclature employed by the earlier physical chemists[2], our term " plain " is not related to a single-term Drude equation. In fact, as discussed elsewhere[6] in detail, Drude equations are of no particular use for the purposes under discussion. While plain curves are distinctly more useful for configurational assignments[12, 13] than monochromatic rotation measurements (usually conducted at the sodium D line), the really important applications of rotatory dispersion measurements lie in the area of anomalous curves.

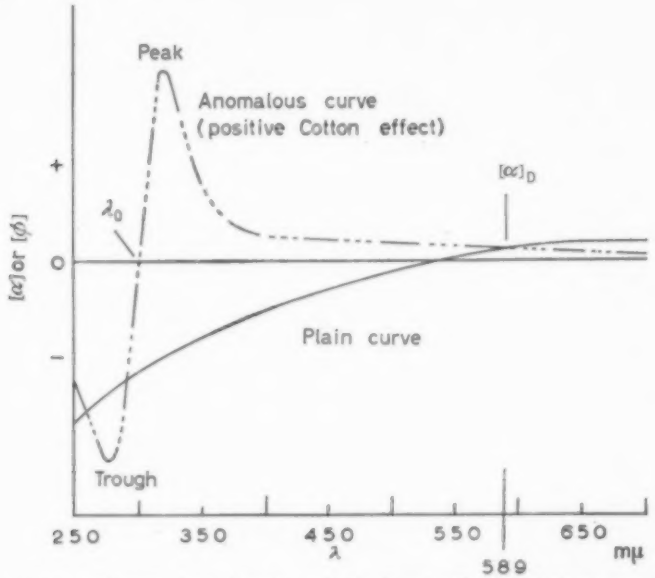


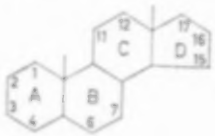
Figure 1. Plain and anomalous (showing positive Cotton effect) optical rotatory dispersion curves

Anomalous curves possess extrema such as peaks and troughs, and a typical example is shown in *Figure 1*. This represents a *single, positive Cotton effect curve*, such as would be exhibited by an optically active substance containing a chromophore absorbing around 300 mμ. It will be noted that the mean of the wavelengths at which the peak and trough occur corresponds approximately to the position (λ_0) of the ultra-violet absorption maximum of this particular substance, and the chromophore, therefore, is considered to be " optically active ". The theoretical basis for such Cotton effect curves is considered in detail elsewhere[6], but it is obvious that, in order to measure such a curve experimentally and to cover the most interesting spectral range (below 350 mμ in *Figure 1*), it must be necessary to determine the rotation through the region of maximal absorption (*ca.* 300 mμ). This is possible

only with weakly absorbing chromophores, and the carbonyl group has proved to be ideal for such purposes. It absorbs in a region of the spectrum (280 – 330 mμ) which is readily accessible with the presently available spectropolarimeters, and it possesses a sufficiently low extinction coefficient for rotation measurements to be conducted through its ultra-violet absorption maximum. The direct relationship between the ultra-violet absorption spectrum and the rotatory dispersion extrema explains why we prefer the terms " peak " and " trough " rather than " maximum " and " minimum ", which are employed in ultra-violet spectroscopy. A rotatory dispersion curve with several extrema (*e.g. Figures 9* and *10*) is called a *multiple Cotton effect curve*. The distance between the peak and trough is referred to as the *amplitude*. As will be shown, the sign (*positive* Cotton effect referring to a curve where the peak occurs at higher wavelength, *negative* Cotton effect to one where the trough appears first in going to lower wavelength), amplitude and shape of the anomalous rotatory dispersion curve can offer much scope for purposes of " fingerprinting ".

Most of the recent work[6] on rotatory dispersion in organic chemistry has been conducted with carbonyl-containing substances, because of the favourable properties of this chromophore and its extremely wide occurrence, notably among natural products. Other chromophores, however, are equally useful, and some of these will be discussed towards the end of the present article. The most important applications of optical rotatory dispersion measurements lie in the areas of relative and absolute configurational assignments (where other physical measurements are of little or no value) and for the solution of conformational problems. In addition, rotatory dispersion can also be employed for structural purposes—such as the location of a carbonyl chromophore in a polycyclic system—and examples of these applications to natural product chemistry will now be presented.

Possibly the most important single reason why structural and stereochemical correlations among ketones by means of rotatory dispersion developed so rapidly was our original choice[1] of steroid ketones as substrates. By taking the steroid molecule (I) and examining the various possible monoketones at positions 1, 2, 3, 4, 6, 7, 11, 12, 15, 16 and 17, it was found[6, 14] that, in many instances, very characteristic rotatory dispersion curves were



(I)

obtained, and that these were not affected by the addition of other, " non-chromophoric " substituents (*e.g.* esters, alcohols, lactones, *etc.*), provided these substituents did not affect the conformation of the parent molecule. We shall return later on to the importance of conformational changes. For instance, in *Figure 2* there are reproduced the rotatory dispersion curves of the 1- (II), 3- (III) and 7- (IV) ketones of the cholestane series, and their respective shapes are so different that they can be used very readily for

VOL. 2 1961

purposes of differentiation. No other physical method presently available can accomplish this.

As a second example, we can consider the three possible points of substitution in ring D of the steroids. Infra-red spectroscopy will enable us to decide immediately whether the carbonyl group forms part of a six-membered (rings A, B, C in (I)) or five-membered (ring D in (I)) ring, but it will not offer definite information about the precise location in that ring. As shown in *Figure 3*, the rotatory dispersion curves of steroidal 15- (V), 16- (VI) and 17- (VII) ketones are again distinct, the very strong negative Cotton effect of 16-keto-steroids being particularly noteworthy.

At this stage it is appropriate to emphasize a point which applies in general to rotatory dispersion as contrasted to monochromatic rotation measurement at the sodium D line (589 mμ). As can be seen in *Figure 3*, the specific rotations of the three ketones (V), (VI) and (VII) at 589 mμ vary by a relatively small factor as compared with the region of their extrema (*ca.* 320 mμ), where differences of several thousand degrees (in

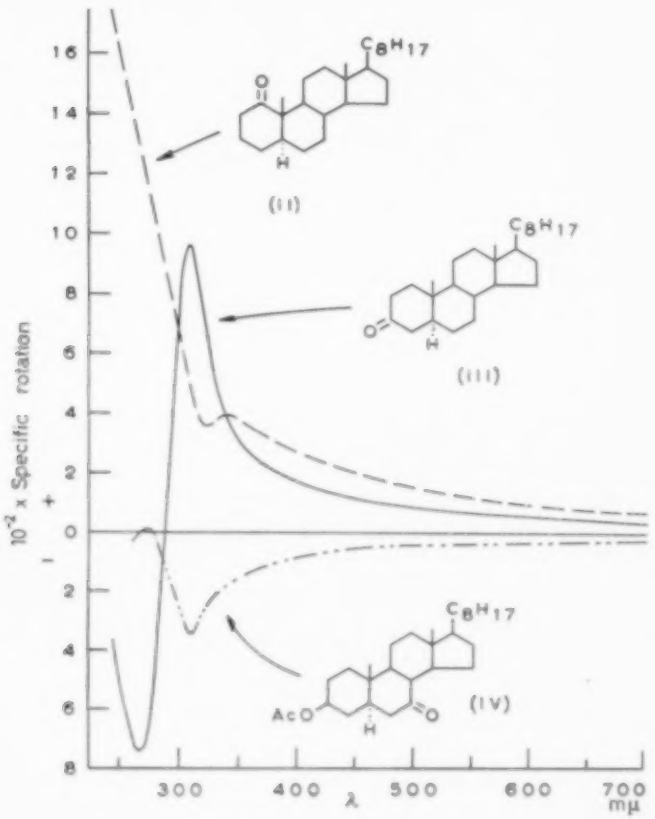


Figure 2. Optical rotatory dispersion curves of 1-, 3- and 7-ketones of the cholestane series

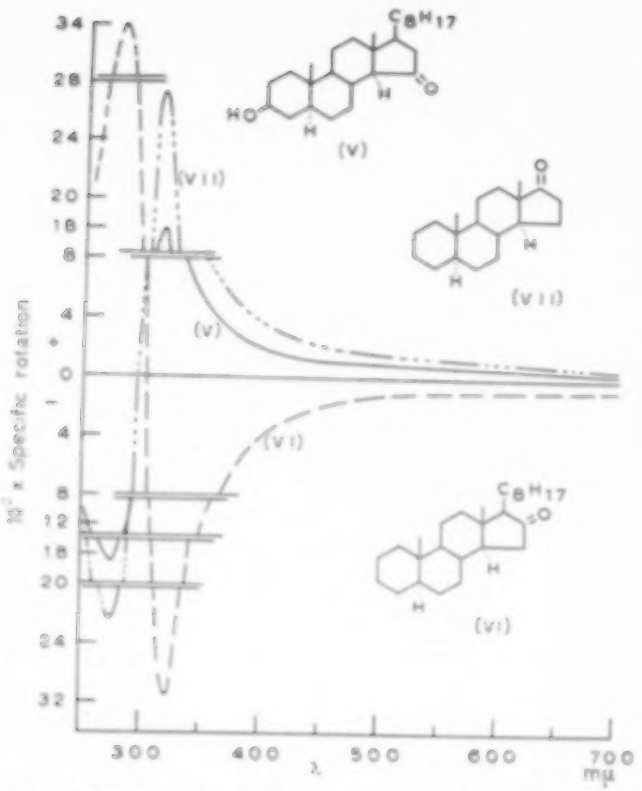


Figure 3. Optical rotatory dispersion curves of 15-, 16- and 17-keto-steroids

terms of specific rotation) may be observed. This has important analytical applications, particularly in kinetic problems[15], where it is possible to carry out precise measurements with approximately one milligramme of material.

In some cases, the rotatory dispersion curves are not sufficiently distinct to be of secure diagnostic value. This is illustrated in *Figure 4* with the rotatory dispersion curve of a 3-keto-steroid, androstan-3-one (VIII) and the corresponding 2-keto- isomer (IX). However, by taking advantage of a simple experimental modification[16], it is easy to differentiate between these two isomers. All that is necessary is to run the rotatory dispersion curve in methanol solution, to add a drop of concentrated hydrochloric acid, and then to repeat the dispersion measurement after a suitable interval. The addition of acid catalyses the formation of the corresponding methyl* ketal (or hemiketal), and, since the latter does not absorb in the 300 mμ region, it will not show a Cotton effect and its rotation will be quite small compared with the peak rotation of the ketone. Any reduction in amplitude,

* Only methanol is suitable for such studies. Ketal formation is greatly reduced in ethanol and completely inhibited in isopropanol[16].

VOL. 2 1961

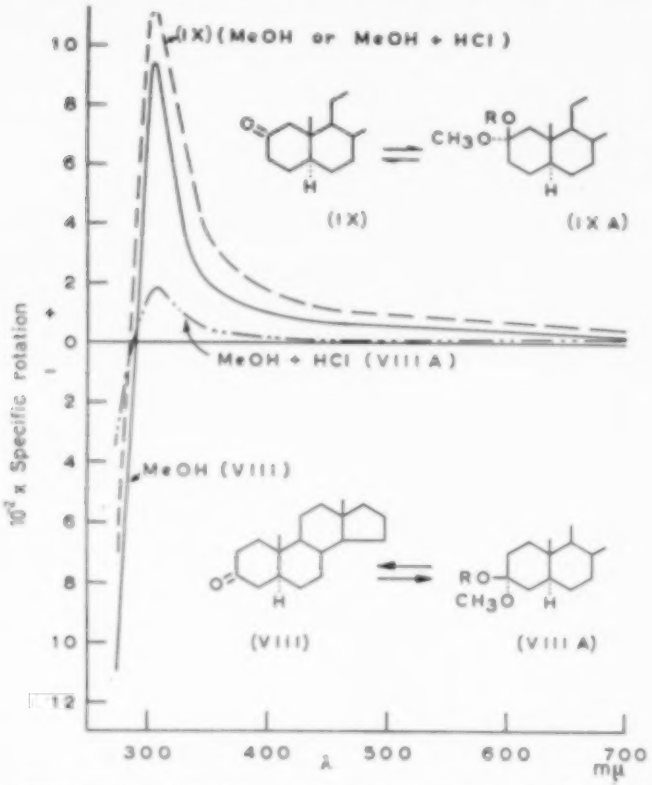


Figure 4. Optical rotatory dispersion curves of androstan-2-one and androstan-3-one, and of their methyl ketals

therefore, offers a semi-quantitative means of determining the extent of ketal production. Extensive studies[16] among 3-keto-steroids (*e.g.* (III) and (VIII)) and the corresponding decalones have shown that the acid-catalysed equilibrium lies on the side of the ketal (VIIIA) to the extent of 64–75 per cent, and that it is extremely sensitive to steric factors. Thus, if the ketal involves a new 1,3-diaxial interaction, not present in the parent ketone, as would be the case in a 2-keto-steroid (IX) and its ketal (IXA), then the equilibrium remains almost completely on the side of the ketone. The Cotton effect amplitude of a 2-keto-steroid (IX), therefore, is essentially unaffected in the presence of hydrochloric acid, and thus offers a sensitive criterion for differentiating between a 2-keto- and a 3-keto-steroid.

Once standard curves have been secured for the various positions in the steroid series, then the location of an unknown carbonyl group in a steroid molecule becomes a relatively simple matter. Similar studies have also been conducted among the tetracyclic[17] and pentacyclic[18] triterpenes, and two illustrations of structural applications of rotatory dispersion measurements in this field will now be offered.

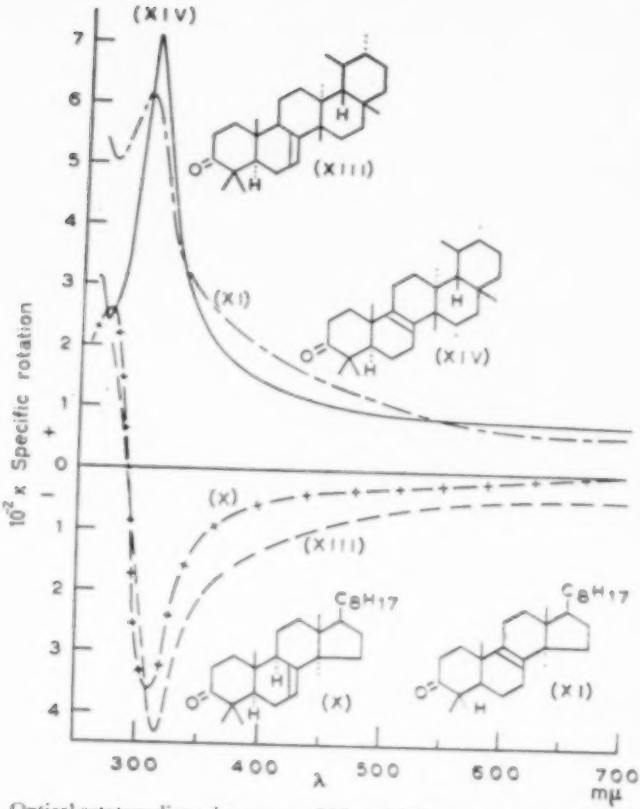
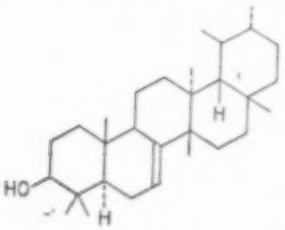


Figure 5. Optical rotatory dispersion curves of Δ^7- and Δ^8-lanosten-3-one, and of bauerenone and isobauerenone

In connection with an examination of the sensitivity of rotatory dispersion to subtle conformational factors, the rotatory dispersion curves of Δ^7- (X) and Δ^8- (XI) lanosten-3-one were measured[17]. In spite of the fact that these two ketones differ only in the location of the double bond, their respective rotatory dispersion curves (*Figure 5*) differ greatly. This has been ascribed[17] to conformational distortion, as has the earlier observed[19] difference in their respective rates of condensation with benzaldehyde. Recent studies by Lahey and Leeding[20] at the University of Queensland have led



(XII)

VOL. 2 1961

to the proposal of the biogenetically intriguing structure (XII) for the triterpene bauerenol. Through the courtesy of Professor Lahey, the rotatory dispersion curves of the derived ketone bauerenone (XIII) and its double-bond isomer isobauerenone (XIV) were measured in our laboratory. Their respective curves (*Figure 5*) bear the same relationship to each other as has been noted[17] in the reference pair Δ^7-lanosten-3-one (X) and Δ^8-lanosten-3-one (XI), thus supporting the earlier structural conclusions[20].

Among ketones of the pentacyclic triterpene series[18], the rotatory dispersion curve of methyl sumaresinonate 3-acetate (XV) exhibited a unique shape, and its curve (*Figure 6*) can thus be considered as a reference standard

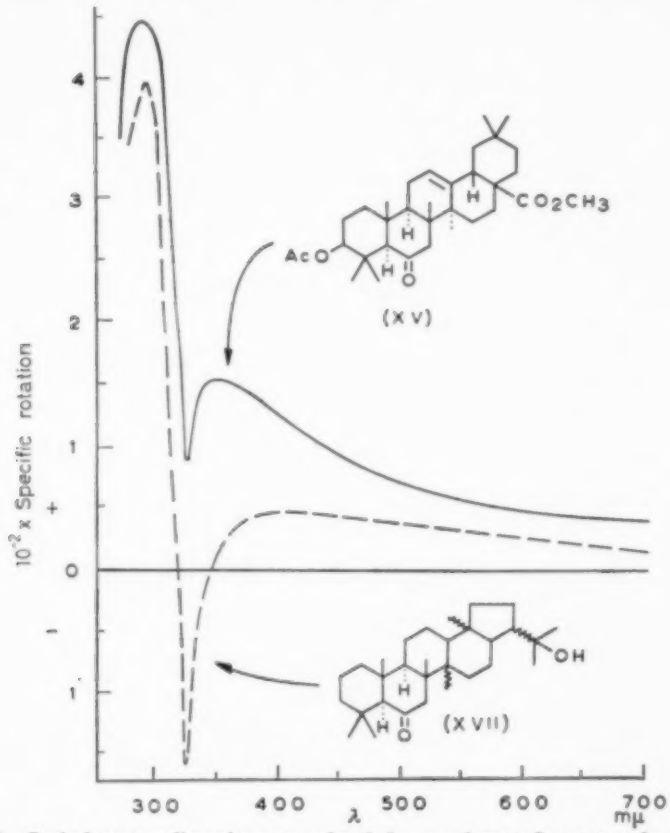
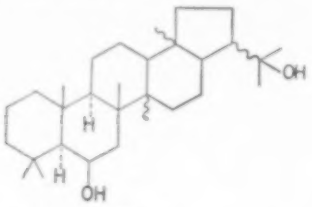


Figure 6. Optical rotatory dispersion curves of methyl sumaresinonate 3-acetate and zeorinone

for 6-ketones among such triterpenoids. Oxygenation in this position of the triterpene skeleton is very rare, but recently Barton and collaborators[21] have presented degradative evidence that zeorin (XVI) bears a hydroxyl group in this position. Since zeorin has so far not been related directly to any other triterpenoid, it was desirable to secure independent support for this structural detail. As shown in *Figure 6*, the rotatory dispersion curve of zeorinone (XVII), kindly supplied by Professor Barton, is so similar in

shape and amplitude to that of the known ketone (XV) of the sumaresinolic acid series that there is little doubt that the carbonyl group is indeed located at C–6. Furthermore, it can be stated with a very great degree of certainty that the hitherto undefined stereochemical arrangement of rings A and B in zeorin (XVI) must coincide with that of sumaresinolic acid and the other members of the β-amyrin class of triterpenes.



(XVI)

The remarkable changes in the rotatory dispersion curves of isomeric ketones differing only in the location of the carbonyl group can be ascribed to the different asymmetric environment in which the carbonyl chromophore finds itself as it is moved around the polycyclic nucleus. Obviously, a change in the asymmetric environment is also produced if the carbonyl group remains in the same location, but its immediate stereochemical

VOL. 2 1961

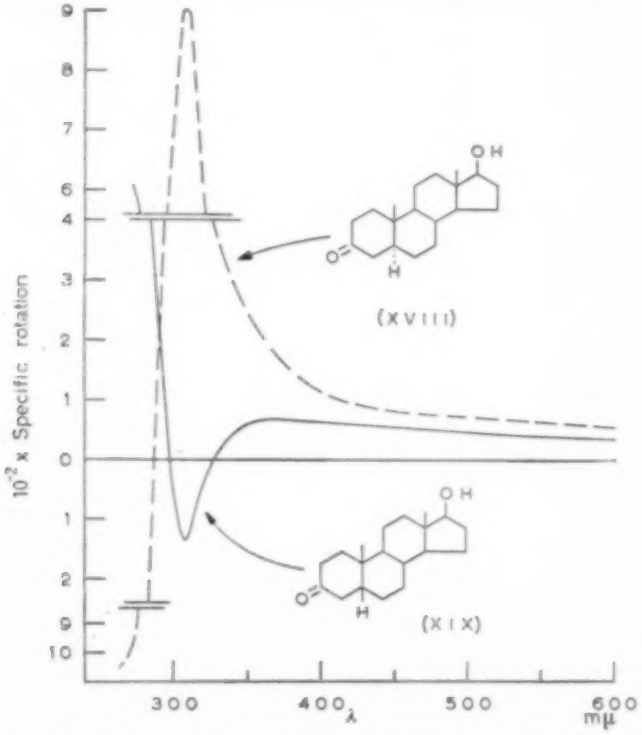
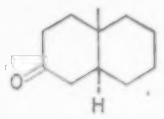
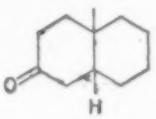


Figure 7. Optical rotatory dispersion curves of 5α- and 5β-androstan-17β-ol-3-one

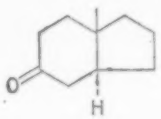
environment is altered. This is illustrated in a striking fashion in *Figure 7*, where it is shown that the rotatory dispersion curves of 5α-androstan-17β-ol-3-one (XVIII) and its 5β- isomer (XIX) actually show opposite sign Cotton effects even though the two ketones differ only in the nature of the A/B ring juncture. These two curves were found[22] to be typical, irrespective of additional non-chromophoric substitution. In fact, the characteristic shapes of these dispersion curves were retained in their bicyclic analogues (XX)[23] and (XXI)[24], and even remained unchanged when the adjacent ring became five-membered as in the hydrindanones (XXII) and (XXIII).



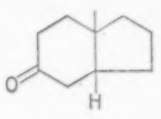
(XX)



(XXI)



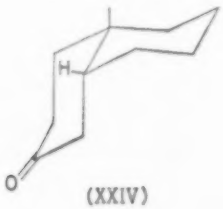
(XXII)



(XXIII)

These results, coupled with many others mentioned in the original papers[23–25], permitted the conclusion that the characteristic shape of a given rotatory dispersion curve of a cyclic ketone is very largely governed by its bicyclic stereochemical environment. The validity of this assumption has been tested by us with numerous substances, and any divergence from this "rule" could invariably be shown to be due to conformational alteration, since this, of course, could affect the asymmetric environment around the carbonyl chromophore.

The above reduction to a bicyclic common denominator has increased greatly the scope of rotatory dispersion measurements, and has made them unsurpassed as far as applications to relative and absolute configurational problems are concerned. A number of examples will be given to illustrate this point, but, before doing so, it is pertinent to mention some other applications of the rotatory dispersion information covered by *Figure 7*. The *cis*-decalone (XXI) can exist in two chair conformations, the "steroid-like" form (XXIV) (steroids such as (XIX) are locked in this conformation by the *trans*- B/C ring juncture) and the "non-steroid" one (XXV). Originally,



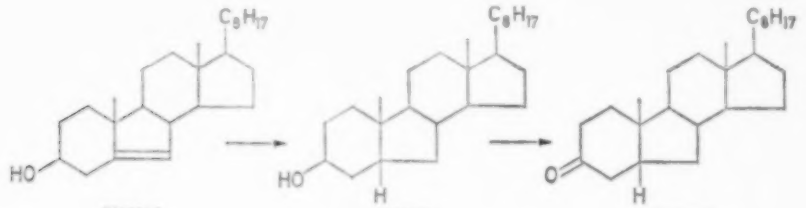
(XXIV)

(XXV)

it was believed[26] that, in the decalone series (XXI), the "non-steroid" conformation (XXV) was the preferred one, but the coincidence of the rotatory dispersion curve of the *cis*-decalone (XXI) with that of the steroid (XIX) of known conformation has led to the decision[24] that the reverse is the case. A similar conclusion can also be reached in the hydrindanone series, since the rotatory dispersion curve of (XXIII) was again of the steroid type ((XIX) in *Figure 7*). It was thus possible to solve a rather

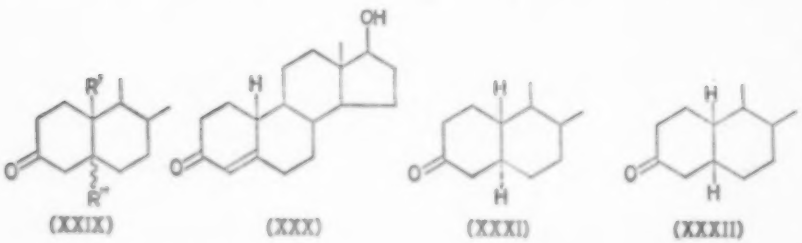
subtle conformational problem in the decalone and hydrindanone series from rotatory dispersion information among steroids.

Conversely, the rotatory dispersion data[25] for the bicyclic hydrindanones (XXII) and (XXIII) offered the first correct information about the stereochemistry of the hydrogenation products of B-norcholesterol (XXVI). The principal product (XXVII)[27], had been oxidized to the ketone



(XXVIII) and its rotatory dispersion curve[25] proved to be of the A/B *cis*-type (XIX). Since studies in the bicyclic series had demonstrated[25] that the size of the adjacent ring does not play an important rôle, provided the stereochemical situation is not otherwise altered, it was suggested by us that the principal product was the 5β-alcohol (XXVII) rather than the anticipated 5α- isomer. This conclusion has since been verified by other studies[28].

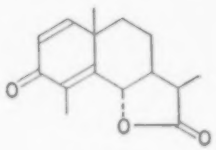
During the past few years, we have measured the rotatory dispersion curves of steroids with a variety of angular substituents ((XXIX), R′ = H, CH_3, halogen; R″ = H, CH_3, OH, CN, CO_2CH_3, $CONH_2$), and in every instance the characteristic rotatory dispersion difference between the A/B *trans*- and A/B *cis*- isomers (see *Figure 7*) was retained, thus offering a tool of unsurpassed value for solving configurational problems of this type. As an illustration, we may cite the reduction of the double bond of 19-nortestosterone (XXX), which with chemical agents[29] leads to one isomer (XXXI) and under catalytic hydrogenation conditions[30] to another (XXXII). The rotatory dispersion curves of these products were typical



of an A/B *trans*- ((XVIII) in *Figure 7*) and A/B *cis*- ((XIX) in *Figure 7*) ring fusion respectively, and thus immediately settled a stereochemical point which, at this time, would not be amenable to attack by any other physical method. A similar problem arose in determining the stereochemistry of certain steroids[31] into which a methyl group was introduced at

C–5 ((XXIX), R′ = R″ = CH_3), and this was again solved in terms of an A/B *cis*- ring fusion by rotatory dispersion measurements.

In the light of the above discussion that the typical rotatory dispersion features of steroid ketones are also retained in their bicyclic analogues, it is



(XXXIII)

not surprising that this tool has been also of great utility in fixing stereochemical details in other molecules. Of the many examples which have been cited[6–8], it may be useful to consider one of the first applications[23] of this approach in the sesquiterpene series.

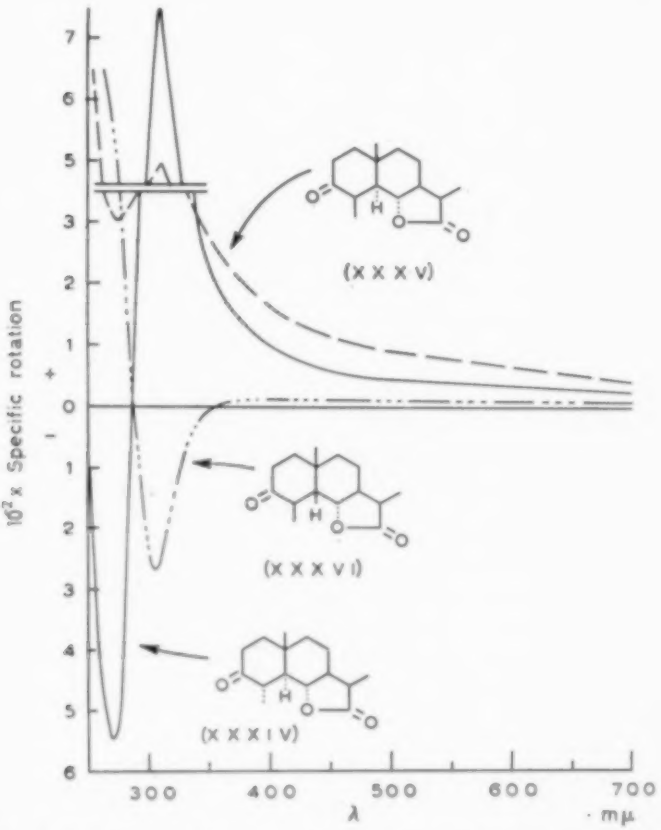
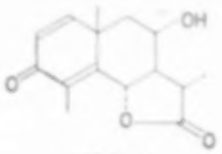


Figure 8. Optical rotatory dispersion curves of three stereoisomeric products formed by catalytic hydrogenation of (−)-α-santonin

Catalytic hydrogenation of (−)-α-santonin (XXXIII) can produce four stereoisomers, of which three ((XXXIV), (XXXV) and (XXXVI)) are readily accessible. Their rotatory dispersion curves are reproduced in *Figure 8*, and it will be noted immediately that the curves of (XXXIV) and (XXXVI) are typical (see *Figure 7*) of an A/B *trans*- and A/B *cis*- junction respectively. Both substances were stable to acid or alkali, thus implying an equatorial orientation for the C–4 methyl group, and this information was sufficient, therefore, to lead to the complete stereochemical assignments[23] expressed in formulae (XXXIV) and (XXXVI). The rotatory dispersion curve of the third isomer (XXXV) was distinct (*Figure 8*), but, since acid or alkali transformed it into (XXXIV), it obviously could differ from the latter only in the orientation of the C–4 methyl group and this can be accommodated only in terms of structure (XXXV). At the time[23] that we made these stereochemical assignments, they were contrary to conclusions then existing in the literature[32], but the correctness of the rotatory dispersion



(XXXVII)

deductions was verified subsequently[23]. The identical rotatory dispersion approach was then employed[24] to determine conclusively the stereochemistry of the hydrogenation products of artemisin (XXXVII).

Until now, the discussion has been limited to saturated ketones. While α,β-unsaturated ketones absorb in the 220–260 mμ region with an intensity which precludes (with the spectropolarimeters available at present) rotation measurements in this region of strong absorption, they also possess a weak absorption band above 300 mμ, which was found[25] to be optically active. The rotatory dispersion curves of such α,β-unsaturated ketones are usually characterized by fine structure which is particularly well resolved in non-polar solvents such as dioxan or octane. An illustration of the typical multiple Cotton effect observed with steroidal Δ^4-3-ketones is given with the rotatory dispersion curve of testosterone (XXXVIII) (see *Figure 9*). Addition of " non-chromophoric " substituents at positions 1, 2, 4, 6 and 7 and in more distant portions of the molecule did not affect this picture, provided these substituents did not result in conformational or electronic disturbances (see below). Even more importantly, extensive measurements in our laboratory of a variety of steroidal, tricyclic and bicyclic ketones with the octalone system (XXXIX) have demonstrated that the nature of the angular substituent can be varied over a wide range ((XXXIX), R = H, CH_3, OH, halogen, CH_2OH, CN, CO_2CH_3) without changing the typical features of the dispersion curve, the controlling factor being simply the configuration of this angular substituent which governs the sign of the multiple Cotton effect. Thus, 19-nortestosterone (XXX), a substance which differs from testosterone (XXXVIII) only in the replacement of the angular methyl group by hydrogen, possesses essentially the same rotatory dispersion

VOL. 2 1961

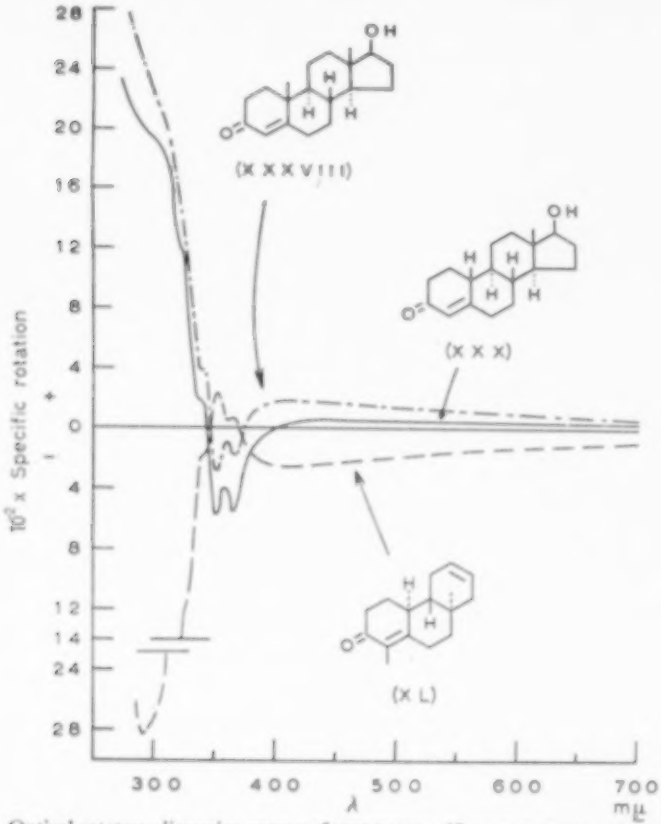
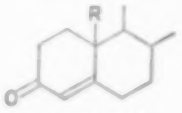


Figure 9. Optical rotatory dispersion curves of testosterone, 19-nortestosterone and a related tricyclic ketone

curve*, while that[35] of the tricyclic ketone (XL)[36] is of mirror-image type since, in terms of its angular substituent it belongs to the antipodal series.

These results would imply that the characteristic rotatory dispersion curve of such octalones (XXXIX) is immune to any type of manipulation. Actually, this is only true if the modifications do not affect the geometrical (conformational) or electronic environment of the α,β-unsaturated carbonyl chromophore. If this is disturbed, then major aberrations in the



(XXXIX)

* This coincidence in the rotatory dispersion curves of 19-nortestosterone (XXX) and testosterone (XXXVIII) represents the most cogent argument for the β-orientation of the C-10 hydrogen atom. Similar rotatory dispersion studies have been carried out to establish this point in other steroidal (C. Djerassi, M. Ehrenstein and G. W. Barber. *Ann.*, **612**, 93 (1958)) and tricyclic (O. Schindler. *Helv. Chim. Acta*, **43**, 754 (1960)) 19-nor- analogues.

rotatory dispersion curve will be noted, even though they may involve only minor structural variations. For instance, the rotatory dispersion curve (*Figure 10*) of 6α-methyltestosterone (XLI) is practically identical with that

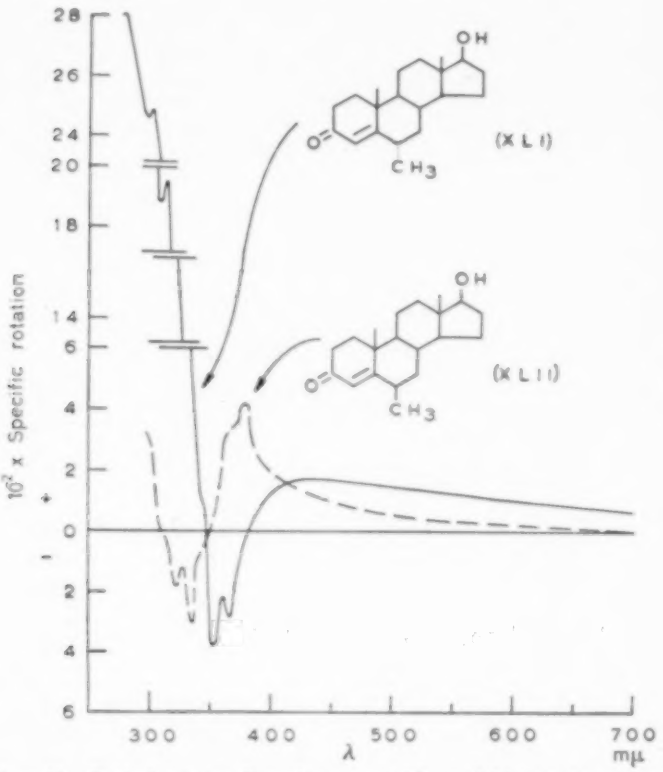
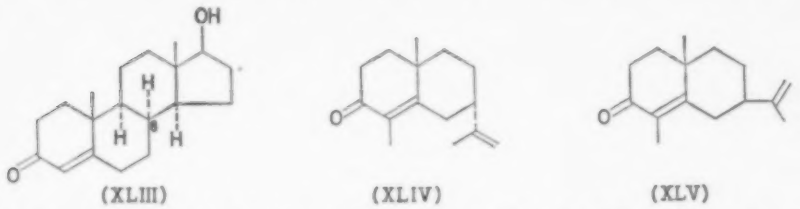


Figure 10. Optical rotatory dispersion curves of 6α- and 6β-methyltestosterone

of testosterone (XXXVIII) (*Figure 9*), while the introduction of an axial substituent as in 6β-methyltestosterone (XLII) produces a drastic change[17] (see *Figure 10*). That this is due to conformational distortion caused by the steric interaction between the axial methyl groups at C–6 and C–10 could be demonstrated[37] conclusively by the synthesis of the corresponding 19-nor-analogue ((XLII), with angular hydrogen atom attached to C–10), in which the original undisturbed rotatory dispersion picture ((XLI) in *Figure 10*) was again restored.

Ample use has been made of the sensitivity of the rotatory dispersion curve of Δ^4-3-keto-steroids to conformational and electronic disturbances accompanying the introduction of axial substituents at C–6 to assign configurations to various 6-alkylated[38], halogenated[39, 40], and nitrated[41] steroids. Variations, similar to those exhibited in *Figure 10*, have also been encountered in 8-isotestosterone (XLIII)[35] (contrasted with testosterone (XXXVIII)) and in epi-α-cyperone (XLIV)[23] (contrasted with α-cyperone

VOL. 2 1961



(XLIII) (XLIV) (XLV)

(XLV)), and in each instance have been associated with conformational alterations (chair to boat) in ring B. The detection of conformational distortion in the axially oriented epi-α-cyperone (XLIV) was particularly striking, and would not have been readily noticeable by other means.

The above discussion may be considered to be the background to perhaps the most significant contribution of optical rotatory dispersion to the armamentarium of the organic chemist, namely the determination of absolute configuration. The subject was first developed in an early paper[23] in our series on *Optical Rotatory Dispersion Studies*, and has since been covered

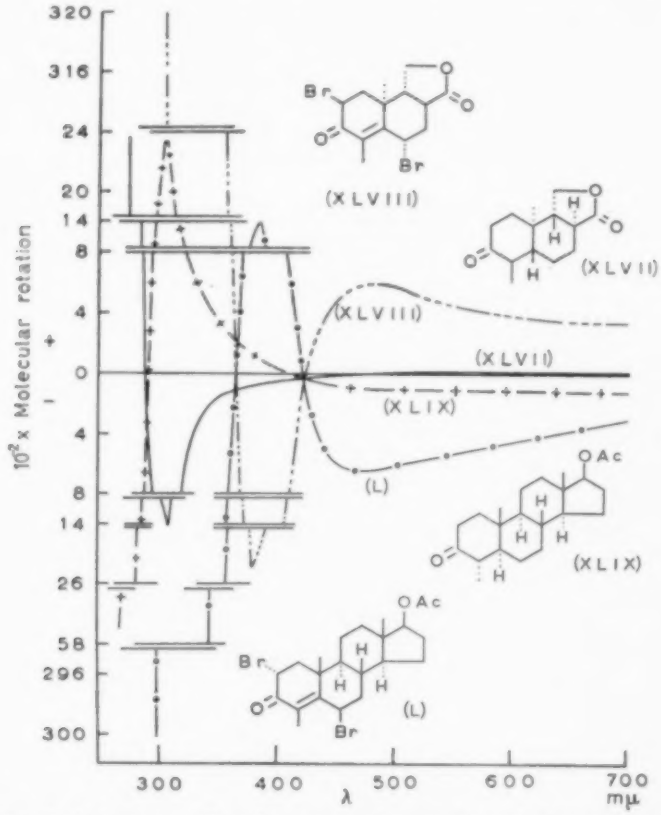


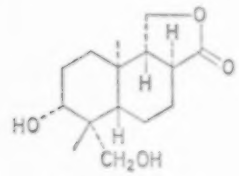
Figure 11. Optical rotatory dispersion curves of saturated nor-ketone and unsaturated dibromo-ketone derivatives of iresin, compared with those of related steroid models

in detail[6,7]. At present, we shall consider only some of the more recent applications of this approach in the natural products field, where it has found immediate and widespread use. We have shown that non-chromophoric substituents play no significant qualitative rôle, the all-important factor being the stereochemical and conformational identity of the appropriate bicyclic environments around the carbonyl chromophore; hence, the rotatory dispersion approach[23] to the determination of absolute configuration consists simply in comparing the dispersion curves of the unknown ketone* with that of a reference compound of known absolute configuration and possessing the appropriate bicyclic system. For many of our initial studies, we have selected steroids as reference substances, as their absolute configurations are known, and virtually all significant bicyclic systems can be found in appropriate steroid substrates.

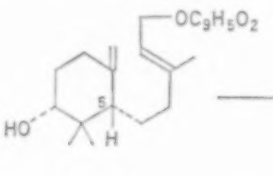
For purposes of illustration of the power and scope of this method, examples will be given where rotatory dispersion has so far offered the only means of arriving at an absolute configurational assignment.

The structure of the sesquiterpene iresin (XLVI) has been established by classical chemical means[42] and confirmed by X-ray studies[43]. Because of the important position of iresin in the biogenetic scheme[44] of the terpenoids, its absolute configuration was clearly of interest, and the problem was solved[45] exclusively by means of optical rotatory dispersion. Iresin (XLVI) was degraded[45] to the saturated nor-ketone (XLVII) and the unsaturated dibromo-ketone (XLVIII), and their respective rotatory dispersion curves were compared with the steroid models (XLIX) and (L), where rings A and B coincide stereochemically and conformationally with the iresin degradation products. As shown in *Figure 11*, the respective pairs (XLVII)–(XLIX) and (XLVIII)–(L) exhibit mirror-image type curves

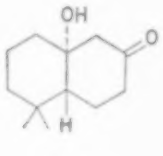
VOL. 2 1961



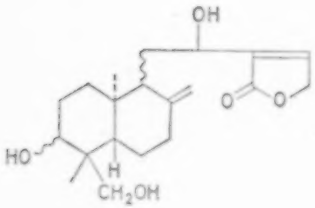
(XLVI)



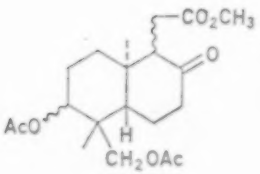
(LI)



(LII)



(LIII)



(LIV)

* Obviously, this statement also applies to other chromophores such as the thione grouping.

whereupon it can be concluded that iresin (XLVI) and its degradation products possess an absolute configuration which is antipodal to that of the steroids. The absolute configuration of the biogenetically related farnesiferol B (LI) was established[46] in a similar fashion by degradation to the bicyclic ketone (LII), and that of andrographolide (LIII)[47] by transformation to the decalone (LIV). Both degradation products (LII) and (LIV) exhibited positive Cotton effects, which could be evaluated by reference to similar Cotton effects (see *Figure 4*) of 2- and 3-keto-steroids of the 5α- series.

The importance of conformational as well as stereochemical identity between the reference substance and the unknown product cannot be overemphasized. Thus, it was noted in an earlier study[17] that introduction of a *gem*-dimethyl substituent into a 3-keto-steroid of the 5α- series resulted in inversion of the Cotton effect, 4,4-dimethylcholestan-3-one (LV) exhibiting a negative one (see *Figure 12*) in contrast to the positive one (see *Figure 2*)

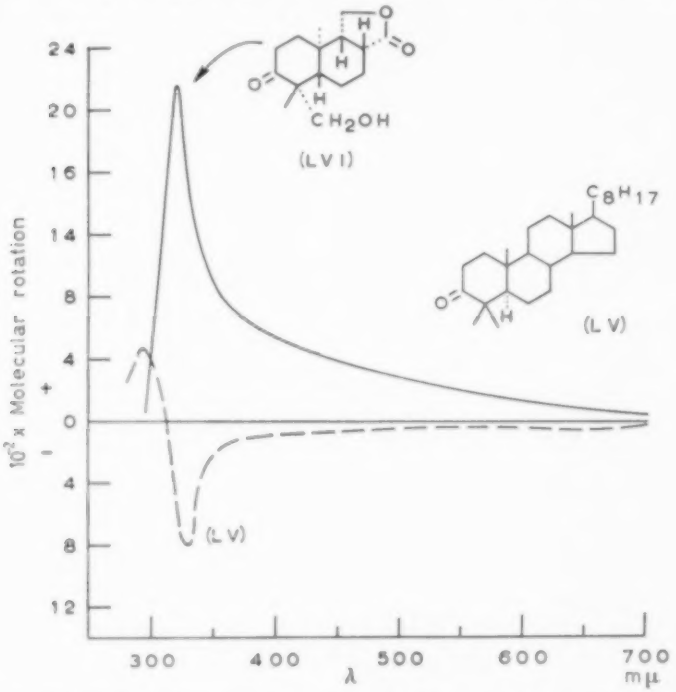
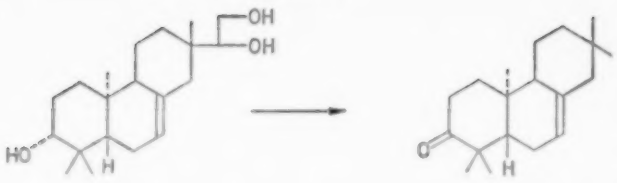


Figure 12. Optical rotatory dispersion curves of 4,4-dimethylcholestan-3-one and dihydroiresone

of cholestan-3-one (III). This behaviour is also observed in 4,4-dimethyl-3-ketones of the 19-nor-steroid series[17], and in fact even among decalones[24], and a possible explanation has already been discussed[17]. If the problem of the absolute configuration of iresin (XLVI) is attacked through the related naturally occurring ketone dihydroiresone (LVI)[48], then an incorrect answer would have been obtained if an ordinary 3-keto-steroid (*e.g.* (III) in



(LVII) (LVIII)

Figure 2) or a 4-monomethyl derivative ((XLIX) in *Figure 11*) had been employed as the reference ketone. However, by using the negative Cotton effect of 4,4-dimethylcholestan-3-one (LV) (see *Figure 12*) for comparison purposes, the correct conclusion with respect to the antipodal nature of the ring juncture of iresin is obtained, since dihydroiresone (LVI) possesses a positive Cotton effect (see *Figure 12*). A similar situation exists in the diterpene darutigenol (LVII)[49*], where its absolute configuration was

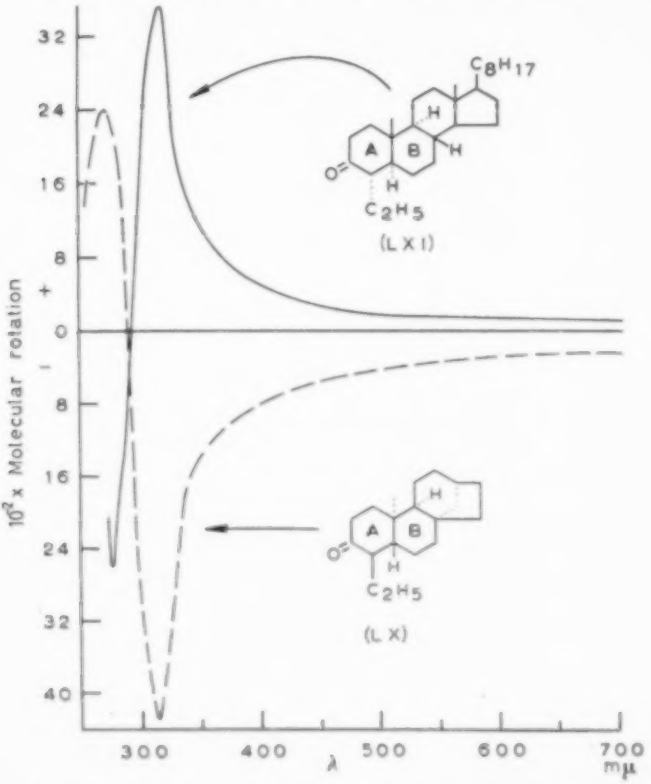


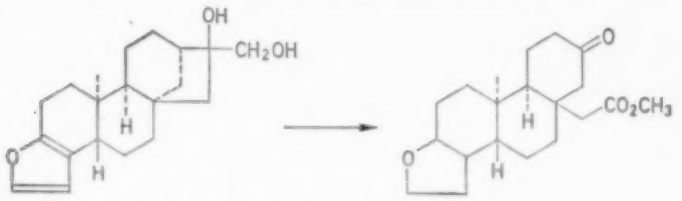
Figure 13. Optical rotatory dispersion curve of a cafestol degradation ketone, compared with that of the steroid reference ketone 4α-ethylcholestan-3-one

* Recent work by A. Diara, C. Asselineau and E. Lederer, *Bull. soc. chim. France*, **1960**, 2171, has shown that the double bond in (LVII) is actually located in the 8—14 position (steroid numbering system). The absolute configurational conclusions, however, are still valid.

VOL. 2 1961

determined by comparing the rotatory dispersion curve (positive Cotton effect) of the derived ketone (LVIII) with the negative Cotton effect of an appropriate 4,4-dimethyl-Δ^7-ketone, Δ^7-lanosten-3-one ((X) in *Figure 5*).

Another pertinent example is the diterpene cafestol (LIX), whose structure had recently been established in our laboratory[50]. Its absolute configuration rests on two different rotatory dispersion arguments. The first[50] pertains to the stereochemistry of the A/B ring fusion, which is assigned a stereochemistry antipodal to that of the steroids since the rotatory dispersion curves (see *Figure 13*) of the cafestol degradation ketone (LX) and the steroid reference ketone, 4α-ethylcholestan-3-one (LXI) bear a mirror-image relation to each other. It should be noted that, for chemical reasons, cafestol (LIX) is believed[50] to possess a *syn*-backbone, in contrast to the *anti*- relationship existing at C–9 and C–10 in the steroids. In order for the rotatory dispersion comparison outlined in *Figure 13* to be valid, it must first be demonstrated that a 9,10-*syn*- arrangement does not affect the characteristic positive Cotton effect (see *Figure 2*) of 3-keto-steroids. This was accomplished by comparing the rotatory dispersion curves of ergostan-3-one and its 9β- analogue, both of them being characterized by positive Cotton effect curves of similar amplitude. There is no doubt, therefore, of the existence of an antipodal A/B ring juncture in cafestol.



(LIX) (LXII)

As far as the stereochemistry of the B/C/D environment is concerned, this rests on several rotatory dispersion arguments, including the positive Cotton effect of the tricyclic ketone (LXII) which was recently obtained[51] from cafestol.

All of the above terpenoids exhibit the outstanding feature of possessing an absolute configuration which is antipodal to that of the steroids. This very unusual point rests completely on rotatory dispersion studies, and it will be admitted that any classical chemical procedure for arriving at an absolute configurational assignment for these substances would have been extremely complicated. It is not surprising, therefore, that this particular rotatory dispersion application has been accepted so quickly in the domain of natural products chemistry; the absolute configuration of as diverse a group as columbin[52], gibberellic acid[53], the ergot alkaloids[54] and limonin[55], just to mention a few recent examples, is based completely on optical rotatory dispersion studies of the type illustrated above.

In connection with our extensive investigations of the rotatory dispersion behaviour of the carbonyl chromophore, it was particularly pertinent to examine α-halogenated ketones, since a number of correlations had already been noted between the orientation of a halogen atom and the position of

the ultra-violet absorption maximum[58] of such α-halogenocyclohexanones. As a result of the initial rotatory dispersion studies[39] of a variety of steroidal α-halogenoketones, an empirical rule was evolved[57] which was called the " axial haloketone rule ". This rule states that introduction of equatorial halogen in either of the positions adjacent to a cyclohexanone does not affect qualitatively the Cotton effect of the parent ketone. On the other hand, axial halogen has a profound effect. First of all, in agreement with earlier ultra-violet spectroscopic measurements[58], the rotatory dispersion curve suffers a bathochromic shift with a concomitant increase in the amplitude of the Cotton effect. Secondly, the sign of the Cotton effect of such an α-halogenocyclohexanone (this applies to chlorine, bromine and iodine, but not to axial fluorine where the opposite effect is noted) can be predicted in the following empirical manner. A model of the cyclohexanone ring is placed in such a manner (see *Figure 14*) that the carbonyl group occupies the " head " of the chair (or boat[59]). By looking down the O=C axis as indicated by the arrow in *Figure 14*, a cyclohexanone with an

(LXIII) (−)Cotton effect (LXIV) (+)Cotton effect

Figure 14. Model of α-halogenocyclohexanone, illustrating the " axial haloketone rule "

axial halogen atom on the left side of the observer (LXIII) will show a negative Cotton effect, while a positive one will be observed if the halogen atom is situated on the right side (LXIV). No exceptions to this rule have as yet been encountered, and it is apparent that, if the absolute configuration of a given axial α-halocyclohexanone is known, its conformation can be established, while conversely the absolute configuration can be deduced if the conformation of the molecule is settled. Several important applications of this rule to structural, conformational and stereochemical problems have already been recorded and these have been reviewed recently[59]. Three examples will suffice to illustrate the power and scope of this rule.

Chlorination of (+)-3-methylcyclohexanone (positive Cotton effect) leads to a crystalline chloro-ketone for which structure (LXV) (or its " flipped-over " chair form (LXVI)) has been established[60]. Allinger and Allinger[61] had already indicated earlier that the conformational equilibrium in the case of 2-bromocyclohexanone is dependent upon the polarity of the solvent, and that the axial form predominates in a non-polar medium (*e.g.* octane), but that in a polar solvent (*e.g.* methanol) an increased proportion of the equatorial form would be expected. Turning now to the specific example of 2-chloro-5-methylcyclohexanone, the form with the equatorial chlorine atom (LXV) would be expected to possess a positive

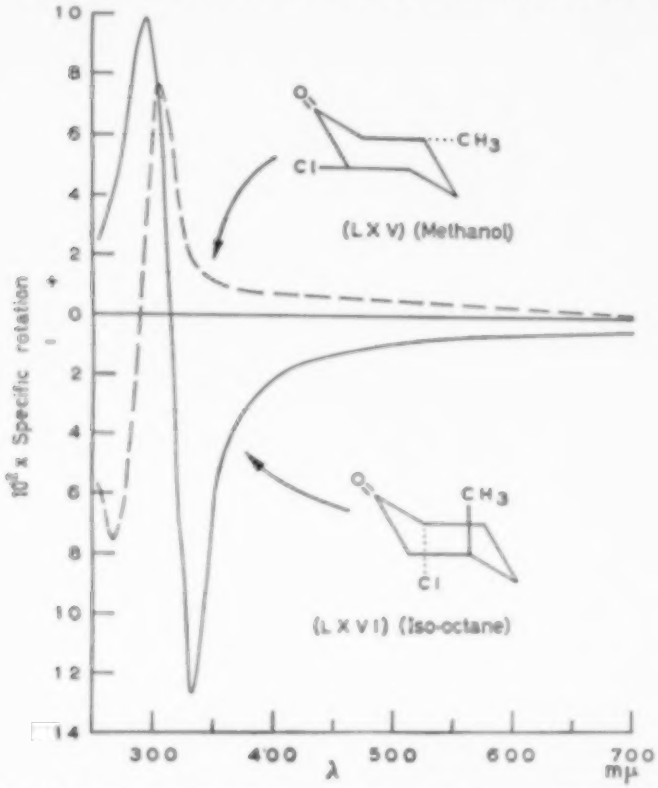
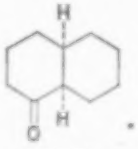


Figure 15. Optical rotatory dispersion curves of 2-chloro-5-methylcyclohexanone in methanol and in iso-octane. The curves represent new measurements in which the spectral range has been extended somewhat over that previously reported[60]

Cotton effect (similar to that of the chlorine-free parent ketone), while the axial haloketone rule would predict a strongly negative Cotton effect for the axial isomer (LXVI). Indeed, when the rotatory dispersion curve of (LXV) was measured in the polar medium methanol, a positive Cotton effect was noted (*Figure 15*) consistent with a predominance of (LXV), while in iso-octane a strongly negative Cotton effect was generated, indicating the increased presence of the axial form (LXVI). *Figure 15* thus represents an excellent graphical illustration of conformational mobility in a cyclohexanone.

Quite recently, we have been able to demonstrate[62] a similar conformational equilibrium in a brominated *cis*-decalone. (−)-*cis*-1-Decalone



(LXVII)

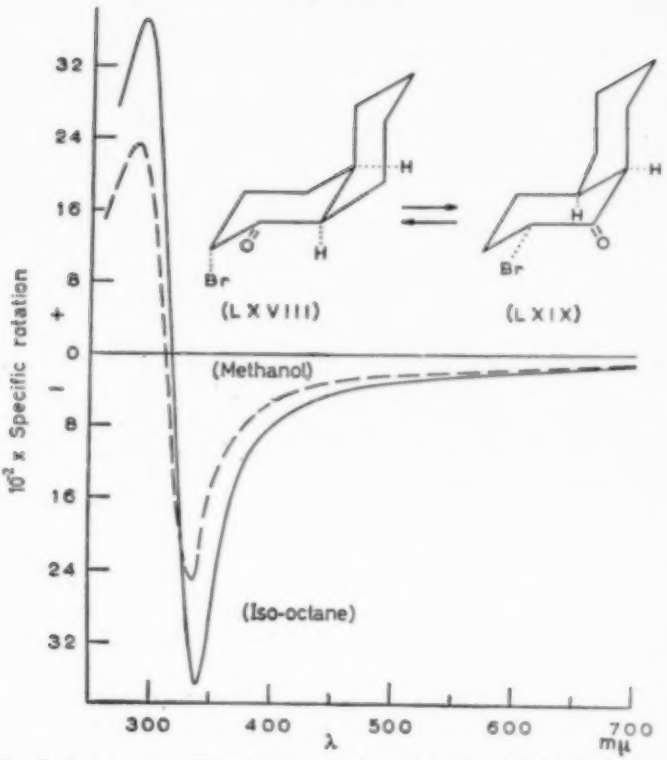
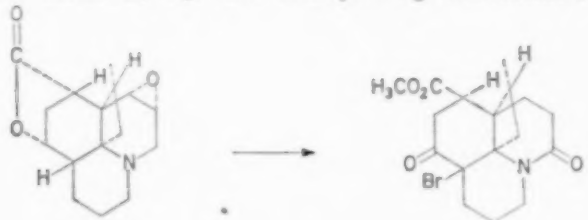


Figure 16. Optical rotatory dispersion curves of (−)-2-bromo-*cis*-1-decalone in methanol and in iso-octane

(LXVII) was converted into the axially oriented (−)-2-bromo-*cis*-1-decalone (LXVIII), whose strongly negative Cotton effect (see *Figure 16*) in iso-octane solution requires that the compound exist in the " steroid " conformation (LXVIII). When the dispersion measurement was repeated in the polar solvent methanol, there occurred a reduction in amplitude, which is only possible if a certain proportion of the " non-steroid " compound (LXIX) with the equatorial bromine atom is generated. That this diminution in amplitude in methanol actually reflects a shift in the conformational equilibrium towards (LXIX) is verified by the observation that other brominated decalones, *e.g.* the corresponding *cis*-9-bromo-1-decalone,



(LXX) (LXXI)

VOL. 2 1961

exhibit rotatory dispersion curves of identical amplitude in either methanol or iso-octane.

The above two examples illustrate the use to which the axial haloketone rule can be put for attacking conformational problems if the absolute configuration is known. The converse—proof of absolute configuration by the axial haloketone rule—is strikingly illustrated by the alkaloid annotinine (LXX), which has recently been transformed[63] into the axial bromoketone (LXXI) possessing a strong negative Cotton effect[64]. Application of the axial haloketone rule shows that this is compatible only with the stereoformula (LXXI), whereupon the absolute configuration (LXX) follows automatically for the parent alkaloid annotinine.

Until now, our discussion has been limited to carbonyl-containing substances, largely because these were the first to be studied by us on the grounds that the carbonyl chromophore has particularly favourable properties for rotatory dispersion studies, and because ketones and aldehydes are among the most widely distributed functional groups. Just as with ultra-violet[56, 65] and infra-red spectroscopy[66], the carbonyl chromophore will continue to occupy a very important place, but it is obvious that other chromophores are available which are optically active and absorb in a convenient spectral region with a sufficiently low extinction to be useful for spectropolarimetric investigations. Many of these potentially useful chromophores have already been reviewed[67], and, at this time, we shall limit ourselves to some recent developments in the natural products field which have been studied in our laboratory.

Apart from the carbonyl moiety, the most widely distributed functional

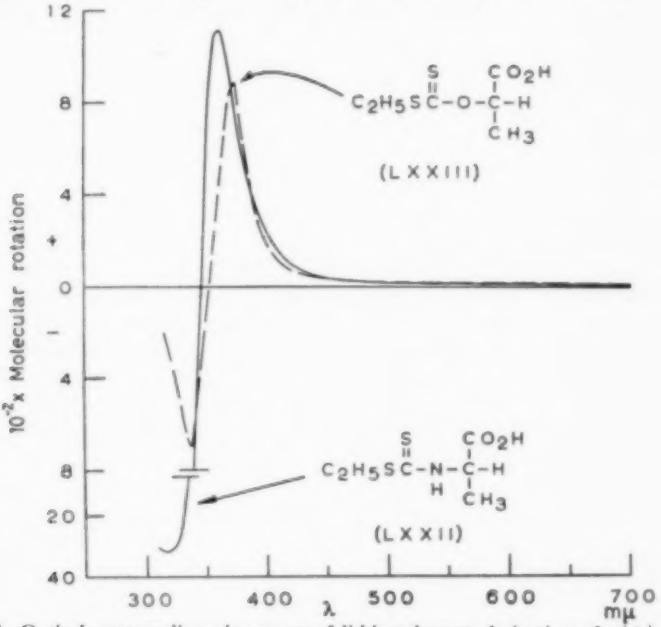
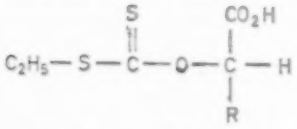


Figure 17. Optical rotatory dispersion curves of dithiocarbamate derivatives of L-(+)-alanine and L-(+)-lactic acid

groups in organic chemistry are carboxylic acid, amine and alcohol groupings. None of these absorbs in a suitable spectral range, and, in order to subject them to the type of rotatory dispersion scrutiny illustrated above for ketones, it is necessary to transform them into derivatives with more favourable spectroscopic properties. The feasibility of this approach can be demonstrated by several examples. Thus we have shown[68] that dithiocarbamate derivatives (*e.g.* (LXXII)) of α-amino-acids (readily prepared by treating an alkaline solution of the α-amino-acid with carbon disulphide and an alkyl halide) absorb near 330 mμ with a very low extinction, and that these derivatives exhibit Cotton effect curves. The same applies to the xanthates of α-hydroxy-acids (*e.g.* (LXXIII)), whose low-intensity ultra-violet absorption maximum falls near 356 mμ. An extensive rotatory dispersion study of a series of such derivatives of α-amino- and α-hydroxy-acids has shown[68] that their rotatory dispersion curves afford by far the most convenient means of establishing the absolute configuration of the α-asymmetric centre, since all members of the L-series exhibit a positive Cotton effect, while a negative one is given by those of the D-series. This is illustrated in *Figure 17* with the rotatory dispersion curves of the appropriate derivatives of L-(+)-alanine (LXXII) and L-(+)-lactic acid (LXXIII), the curve of the latter being displaced somewhat to the visible, since its ultra-violet absorption maximum occurs approximately 30 mμ closer to the red than that of the dithiocarbamate (LXXII). The nature of the α-alkyl substituent is not important, since α-hydroxy-acids such as L-(−)-malic acid and L-(+)-mandelic acid behave in an identical fashion, their respective xanthates ((LXXIV) and (LXXV)) exhibiting positive Cotton effect curves even though the parent acids show D line rotations of opposite sign.



R = $CH_2—CO_2H$ (LXXIV)

R = C_6H_5 (LXXV)

The simplicity of this rotatory dispersion approach can be contrasted with the substantial difficulties which were encountered in the classical proof of absolute configuration of mandelic acid[69].

As far as applications in the α-amino-acid field are concerned, the method should not only be useful for establishing the absolute configuration of new α-amino-acids that may be discovered in the future, but also for determining the configuration of a terminal amino-acid in a peptide, a problem which is particularly pertinent in the antibiotic field. In support of this statement may be cited the observation[68] that the dithiocarbamate derivatives of L-alanyl-L-alanine and L-alanyl-D-alanine exhibit positive Cotton effect curves of identical amplitude, the governing factor being the stereochemistry of the α-asymmetric centre to which the free amino-acid group is attached.

Some time ago, Kenner and Khorana[70] suggested *N*-thioncarbethoxy-α-amino-acids (*e.g.* (LXXVI)) as suitable intermediates for peptide degradation. Their work was limited to the preparation of such derivatives in the DL-series, but preparation of the optically active derivatives and optical rotatory dispersion measurements[71] have shown that *N*-thioncarbethoxy-α-amino-acids of the L-series (*e.g.* L-leucine derivative (LXXVI)

in *Figure 18*) exhibit positive Cotton effect curves, similar to the analogous dithiocarbamates (LXXII).

The spectroscopic properties of the C=S chromophore have proved to be useful in a number of environments. Thus, Owen and collaborators[72] have prepared several trithiocarbonates in the carbohydrate field. These derivatives are characterized by a low-intensity absorption band at 450 mμ, which was shown to be optically active. Several members of this class have already been studied in our laboratory, and, as an example, there is reproduced in *Figure 18* the positive Cotton effect exhibited by 5,6,dideoxy-1,3:2,4-di-*O*-ethylidene-5,6-(thiocarbonyldithio)-L-iditol (LXXVII).

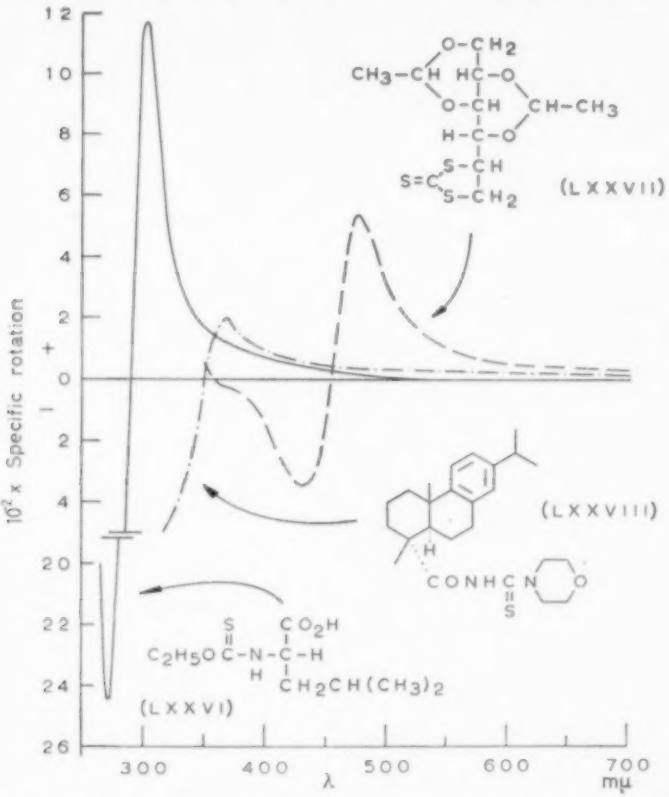


Figure 18. Optical rotatory dispersion curves of *N*-thioncarbethoxy-L-leucine, 5,6-dideoxy-1,3:2,4-di-*O*-ethylidene-5,6-(thiocarbonyldithio)-L-iditol, and a thiourea derivative of dehydroabietic acid

In a search for derivatives of carboxylic acids[73] which will exhibit Cotton effect curves suitable for configurational correlations, we have selected[74] certain acylthioureas. Of particular utility proved to be the thioureas obtained upon successive treatment of an acid chloride with potassium thiocyanate and morpholine. In *Figure 18*, there is shown the positive Cotton effect of such a derivative (LXXVIII) (λ_{max} = 340 mμ) obtained from dehydroabietic acid. The synthesis and optical rotatory dispersion

curves of a variety of such acid derivatives are now under way in our laboratory, and the results to date suggest that this approach will be useful for assigning configurations to the α-asymmetric centre of optically active carboxylic acids.

My somewhat cursory review of the present position of optical rotatory dispersion measurements in the natural products field has shown that, in a period of less than five years, this physical tool has become an important adjunct to investigations in this area. A great deal of research is now going on in a large number of laboratories on various practical and theoretical applications of rotatory dispersion to the entire field of organic chemistry. It is very unlikely that research on optical rotatory dispersion on the part of organic chemists would have proceeded so rapidly, and been accepted so generally, were it not for the fact that a variety of suitable test substances was available from the field of natural products. Indeed, in the development of no other physical method have natural products played so essential a rôle as in optical rotatory dispersion.

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VOL. 2 1961

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THE DIRECT DETERMINATION OF THE MOLECULAR STRUCTURES OF NATURAL PRODUCTS

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INTRODUCTION

When I came to look again at the title of my talk, it appeared to me that it had not quite succeeded in defining the scope of my subject adequately. Let me say, therefore, that my purpose is to show that, given the empirical formula of a suitable derivative of a natural product in a satisfactory crystalline form, it is possible to arrive at the three-dimensional molecular structure in a direct manner and with only minimum assumptions, these being of a general type.

The task of preparing this lecture was influenced, although not made easier, by the increase in the numbers of moderately complex molecules which have been subjected to X-ray analysis in the last few years. It appears probable that this increased interest (particularly in natural products) is not a passing phase, but a consistent change in attitude which may lead, by its results, to a reconsideration of the rôle of X-ray analysis in this field. Prospects exist for the growth of specialist groups to determine structures of natural products by the application of this technique.

There is little need to dwell on the reasons for determining molecular structure—such information is basic to any understanding of how molecules can be chemically modified with intention and how they may be interrelated biogenetically. Although two-dimensional structural formulae have served well in the past, it is clear from the extensive discussion of the influence of conformation and the increased interest in absolute configuration that a fairly detailed three-dimensional picture of the molecule is now required. This being so, the determination of molecular structure in such detail is the essential first stage in the study of a new compound and one which must be solved in as direct and rapid a way as is consistent with accuracy. A solution by classical methods through chemical degradation, and then confirmation by synthesis, offers an attractive and exciting task for many organic chemists; but even for moderately complex compounds, the number of man-years involved in the first step, *i.e.* solution of the structure, is becoming burdensome, particularly for those compounds with inter-linked ring systems—*e.g.* the recent description of the chemical constitution of limonin which involved 14 authors[1]. In this field, X-ray structure analysis may occupy a unique rôle since, with certain conditions satisfied, it can be of general application. It is one in which the latent power of computers may be very effectively placed at the service of organic chemistry.

I want to illustrate, by selected examples, how X-ray analysis has been of help in this aspect of organic chemistry, with particular reference to natural products[2–5], and how the co-ordination of facilities has greatly increased the prospect of this assistance in the future. To do so, we need first to deal with certain of the features which render the X-ray method peculiarly suited to this task.

The physical methods of determining molecular structure fall into two general types, and it is useful to appreciate the clear distinction between them. The first group deals with " fragmentary " information, *i.e.* it gives information primarily about " bits " of the molecule (groups or radicals). Of such techniques, the main representative is that which measures changes in energy between the states of a molecule—ranging from ultra-violet through to microwave absorption. In many respects, these techniques resemble chemical degradative methods which also yield " fragments ", recognition of which permit these " fragments " to be fitted together to derive the molecular structure. Perhaps because of this similarity, the organic chemist has been quick to appreciate and accept these techniques and make wide application of them. The second type of physical method is the diffraction technique which, by contrast with the first group, does not offer partial information—it represents an all-or-none approach to molecular structure. Wide use has not been made of this technique in the past but, as a result mainly of the availability of large electronic computers, this attitude may be changing. For this reason now is an appropriate time to indicate the scope of the technique.

VOL. 2 1961

X-RAY ANALYSIS

Outline of the X-ray method

With regard to this aspect of the all-or-none approach, we may consider the diffraction of X-rays by a single crystal, taken over all orientations. Experimentally, we end up with an array on films of spots of varying intensity, each spot being related to a set of parallel planes in the crystal referred to by their Miller indices, *hkl*, and its intensity being related to an amplitude value, $|F|$. So we have an extensive list of measurements, $|F(hkl)|$. These arise from the periodic smooth distribution of electron density within the crystal, $\rho(xyz)$, where x, y, and z are fractions of the repeat distances of the unit cell $a.bxc$. There are two relationships, (1) and (2), between these quantities.

$$\rho(XYZ) = \frac{1}{V}\sum h \sum_{-\infty}^{+\infty} k \sum l\, F(hkl) \exp\left\{-2\pi i(hX + kY + lZ)\right\} \tag{1}$$

$$F(hkl) = V_c \int\int\int \rho(xyz) \exp\left\{2\pi i(hx + ky + lz)\right\} \mathrm{d}x\mathrm{d}y\mathrm{d}z \tag{2}$$

$$\equiv \sum_r f_r(hkl) \exp\left\{2\pi i(hx_r + ky_r + lz_r)\right\} \tag{2a}$$

It is not our intention to explain here in any detail the two distributions, $\rho(xyz)$ and $F(hkl)$, except to point out that their relationship is a mutually

dependent or reciprocal one. Thus, in a strict sense, to find out about one structure factor, $F(hkl)$, we need to know all about $\rho(xyz)$, *i.e.* the contents of the unit cell, with reasonable precision. Conversely, to determine the value of the electron density ρ at any given point x,y,z in the unit cell, we need all the $F(hkl)$ values. It is evident, therefore, in the approach imposed by this technique, that the available experimental information—the $|F|$ values—cannot be treated piecemeal. We must determine all atom positions to be completely satisfied with, and certain of, our end-result. Fortunately, the X-ray method does not demand a one-step deduction of the completely correct structure, but is amenable to a gradual approach to the true solution by iterative processes.

So far, then, the procedure appears straightforward. It is a matter of collecting the $|F|$ data and combining them according to equation (1). However, this conceals the fact that each F can be a complex quantity, $|F|\cos\ \alpha + i\ |F|\ \sin\ \alpha$, and two parameters are necessary to define F, namely the modulus, $|F|$, and the phase angle, α. We can measure $|F|$, but, in general, cannot determine α experimentally for a single crystal using one radiation. Should the crystal contain a centre of symmetry, then α reduces to 0 or π, *i.e.* F may be $+F\ (\cos 0°)$ or $-F(\cos \pi)$. If, however, the structure is asymmetric, as is extremely probable for a natural product, then α may range from 0 to 2π, and it is obvious that the situation becomes complex. The possibility of a practicable solution of the crystal structure is then closely bound up with the size of the molecule and the number of molecules constituting the asymmetric unit, *i.e.* the total number of atomic parameters that must be determined. As to the various proposals for the solution of the general phase problem, *i.e.* for any arbitrarily selected crystal, I must refer you to more extensive treatments[6], but here, if we set ourselves the more limited task of determining certain organic structures with some prospect of success, we must narrow our field to consideration of the "heavy atom" method as a means of yielding a first approximation to the phase angle. This does not mean that other methods cannot be used to solve such structures, *e.g.* hydroxydihydroeremophilone[7], but to use them must involve a certain amount of chemical information, and, further, they are not yet adequately developed to deal with complex asymmetric structures. The heavy-atom method offers the possibility of determining a structure with the minimum of assumptions and the minimum of chemical knowledge, and, because of these conditions, parts of the process can be made automatic. In principle, the restrictive conditions of the heavy-atom method mean that we cannot tackle any crystal offered, but must select a suitable derivative which contains one or more (but not too many) atoms of atomic number higher than those constituting the main bulk of the molecule, *i.e.* C, N and O. For the small sacrifice of the added complexity of the heavy atom(s), we gain a more certain starting point in analysis.

The relative weight of the heavy atom

In considering the general strategy for the structure determination of a compound of natural origin, the question arises as to what is the most suitable weight of the heavy atom with respect to the remainder of the

molecule. Choice is frequently restricted by chemical considerations or the crystallizability of derivatives, but some numerical estimate is useful. There are several factors involved. The value of $|F|$ is formed of a vector sum of the atomic contributions (see equation (2)) which, for convenience, we may consider in two parts—that due to the N heavy atoms NA_H, and that due to the n light atoms nA_L in which we are mainly interested since they constitute the molecular skeleton(s). The use of a very heavy atom will, by itself, give a very close approximation to the " true " phase angle, but due to the error inherent in the measurement of $|F_0|$ (5–10 per cent), we will not gain very exact information on the contribution of A_L. On the other hand, if A_H is not heavy enough, then there may arise uncertainties during the analysis which may retard progress—in the extreme, the analysis may not be able to start since it may not be possible to locate A_H with certainty in the first stage. A useful measure for selection in compounds of moderate complexity is given by $\Sigma^{N} Z_H^2 / \Sigma^{n} Z_L^2$, where Z_H and Z_L refer to the atomic number of the " heavy " and " light " atom types respectively. Values for typical analyses[4] cover a wide range with a mean value near 1·0. Values above 2·0 have been used, but, for the vitamin B_{12}—SeCN derivative[8], a value of 0·46 (based on Co + Se) sufficed, and an even lower value of 0·22 (for S) in tosyl-prolyl-hydroxyproline[9] permitted a successful analysis. Given the choice, it is preferable to veer on the low side, 0·6–0·8. The heaviness index does not provide a complete answer, since the heavy-atom technique depends also on the change in distribution of the magnitudes of $|F|$ with increasing number of atoms (see *Figure 2* in a review by the author[4]). This factor becomes of greater importance as the molecular size increases, and its significance is clear in the case of haemoglobin[10] and myoglobin[11] heavy-atom derivatives for which the heaviness index is extremely small. However, for the range of molecular size being considered here, the index is a useful guide*.

Experimental conditions

A successful analysis is not dependent only on the choice of a suitable derivative as indicated by the heaviness index, but is intimately tied up with the range and quality of the diffraction data. This aspect need be mentioned only insofar as it influences the analysis both as to speed of solution of the structure and the accuracy of the refinement. It is useful to revert to equations (1) and (2) to note a second aspect of their reciprocal relationship, *i.e.* between the shapes of atoms in real space (in terms of the electron density, ρ) and the distribution of the diffraction data, $F(hkl)$. For an isolated atom, the distribution in diffraction space is compared with the shape of an isolated atom in real space in *Figure 1*. The broader the peak in diffraction space which corresponds to more extensive diffraction data, the sharper is the atom peak in real space, and hence it may be more readily and accurately located. Conversely, where the range of data is limited, the peak in real space is very diffuse. For adjacent atoms, the ability to site them accurately depends on the ability to differentiate them into separate peaks (see *Figure 1* (*a*) (*iii*) and (*b*) (*iii*)). For most organic

* More elaborate discussions of the influence of the heavy atom in determining phase (or signs) have been given by Luzzati[12], Woolfson[13] and Sim[14].

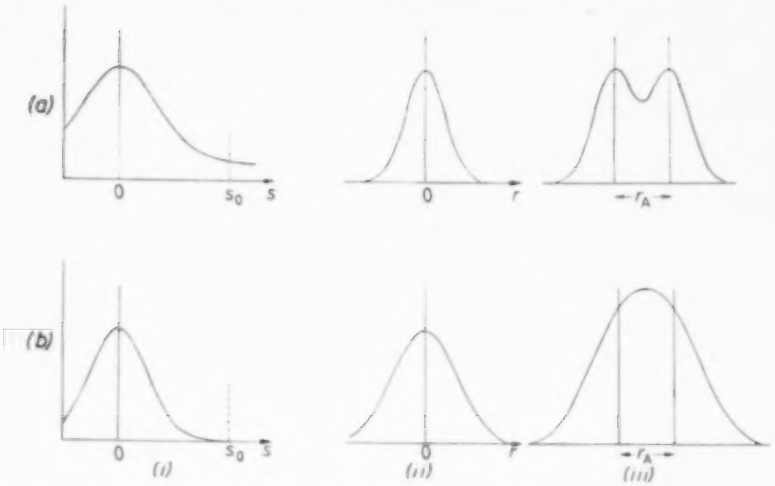

Figure 1. Comparison of the influence of (*a*) small and (*b*) considerable thermal motion on the distribution in (*i*) diffraction space and (*ii*) real space for an isolated atom. (*iii*) compares the corresponding distributions in real space of two atoms of the same shape as in (*ii*) separated by r_A. The experimental limit of recorded diffraction data is s_0

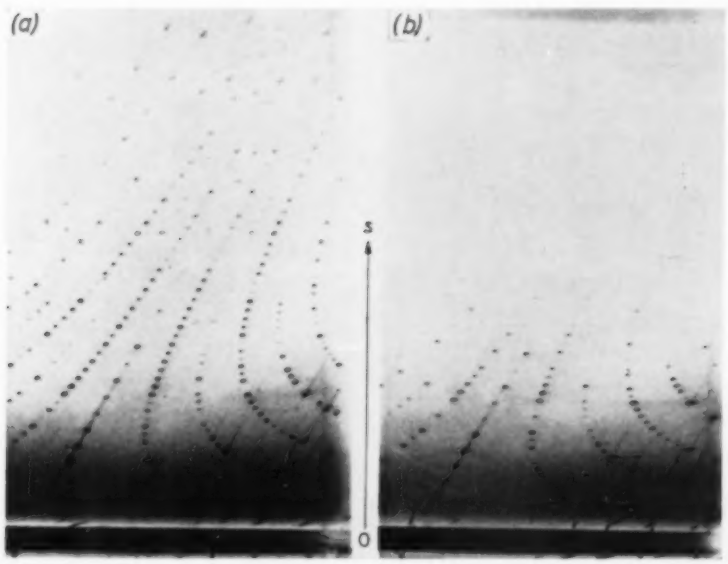

Figure 2. Comparison of a zero-layer Weissenberg photograph of lanostenyl iodoacetate (*a*) at − 160°C and (*b*) at 25°

compounds, the molecules and the atoms thereof are subject to considerable thermal vibration at room temperature, and the situation is more in accord with *Figure 1* (*b*), the diffraction data falling off very rapidly with increasing angle. The possibility exists of changing this situation experimentally to the more advantageous case, *Figure 1* (*a*), by lowering the temperature of the crystal, thus reducing thermal vibration of the atoms and extending the range of diffraction data. Temperatures of the order of −150 to −180°C are readily obtained by the use of liquid air[15], while lower values are feasible if liquid hydrogen or helium is available[16]. The improvement which is possible is shown dramatically in *Figure 2*.

The second aspect of the experimental data is the magnitude of the $|F_o|$ terms. For a given exposure, only a certain proportion of reflections will be recorded, all others lying below the background value or limit of visibility. To ensure that the maximum data are recorded so that amplitude termination will not influence results, the exposure must be the maximum practicable—an important factor for complex molecules if the analysis is being carried out with three-dimensional data. For a normal X-ray generator, it is not uncommon with crystals of natural product origin for each layer, of which there may be 5 to 20, to be exposed for 200–250 h, and thus the collection of the data becomes a major time-component of the analysis. To overcome this, the time factor can be reduced by the use of a high-power X-ray generator[17].

Because of the importance not only of the maximum amount of data but also of its full population over the whole observational range, a combination of a low-temperature adaptor with a high-power generator provides a considerable improvement in the range of data and the speed of collection. Thus, for the analysis of himbacine hydrobromide[18], it has been found possible to record the selected 6 layers in 5 days, each exposure being from 5 to 8 h and the percentage population recorded being 90 per cent.

So far, photographic techniques of collecting intensity data have been implied. The accuracy of measurement is of the order of 5–10 per cent and, for greater accuracy, it would be necessary to use counter techniques of measuring intensities. For complex molecules with large numbers of $|F|$ values, *e.g.* 2927 for vitamin B_{12} (wet)[19], 3351 for the hexacarboxylic acid from vitamin B_{12}[20] and 3400 for jacobine bromohydrin[21], it would require to be an automatic or semi-automatic process. Several designs have been proposed[22], and it is very probable that with increased need there will be an increased effort to make this aspect of structure analysis automatic.

Space groups – $P2_1$ and $P2_12_12_1$

Before considering the methods used to extract structural information from the diffraction data, it is informative for this later purpose to mention the three-dimensional spatial arrangements which molecules adopt when persuaded to crystallize. There are 230 spatial arrangements (space groups) which are theoretically possible, but natural products crystallize in only a very limited number of these. Since the molecules of natural products are generally asymmetric and, in addition, have little internal symmetry, it is found in practice that the majority crystallize in one or other of only two

VOL. 2 1961

space groups of the 138 theoretically available asymmetric space groups—either the monoclinic $P2_1$ or the orthorhombic $P2_12_12_1$ (see *Table 1*). The many analyses of amino-acids, peptides, sugars, purines and pyrimidines have been omitted from the list in *Table 1*. This decision is arbitrary but appears valid for the author's purpose in that, for the majority of such compounds, their molecular formulae were not in doubt, details of conformation and configuration being the principal aim of the analyses.

Since the tactical approach to the solution of the structure is influenced by the space group in which it crystallizes, and since these two space groups dominate the field, we shall draw attention to certain of their features and mention conditions imposed by their detailed symmetry. The relationships of the symmetry elements and asymmetric units are shown in *Figure 3*.

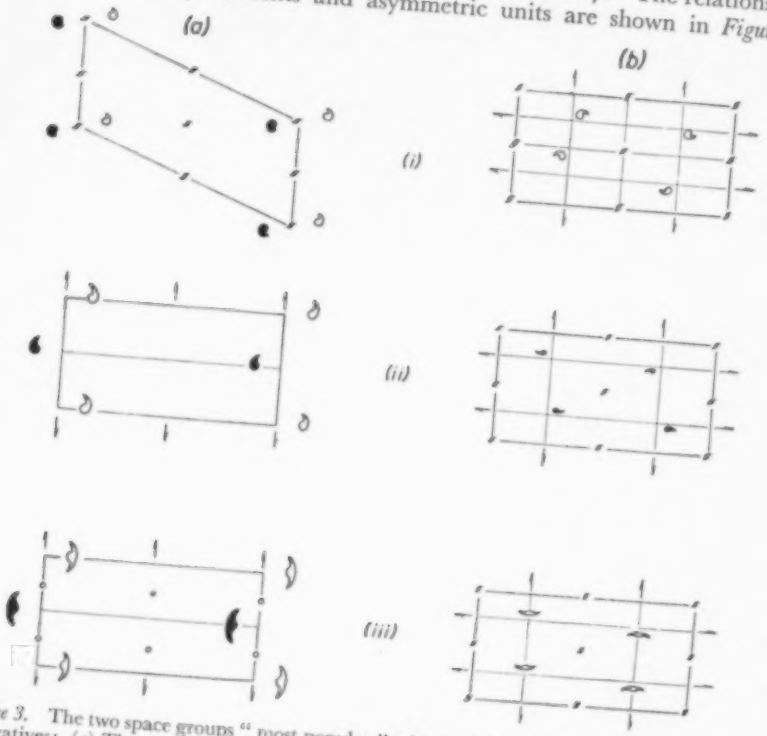

Figure 3. The two space groups " most popular " with crystals of natural products and their derivatives: (*a*) The monoclinic space group $P2_1$: (*i*) as viewed down the *b* symmetry axis; (*ii*) as viewed down the *a* axis; (*iii*) a symmetrized projection of (*ii*) due to phasing with a heavy atom. (*b*) The orthorhombic space group $P2_12_12_1$: (*i*) as viewed down the *a* axis; (*ii*) as viewed down the *b* axis; (*iii*) a symmetrized projection of (*ii*) due to phasing with a heavy atom in a special position

The symbols used for symmetry elements are standard (see *International Tables for X-Ray Crystallography*, Vol. I (1952)). For $P2_1$, the situation is simple—deceptively so from a structural aspect. There is only one type of symmetry element and only one set of these—two-fold screw axes parallel to the *b* axis. There are only two asymmetric units in the unit cell, *i.e.* given one unit or molecule then the other unit or molecule can be described as

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VOL. 2 1961

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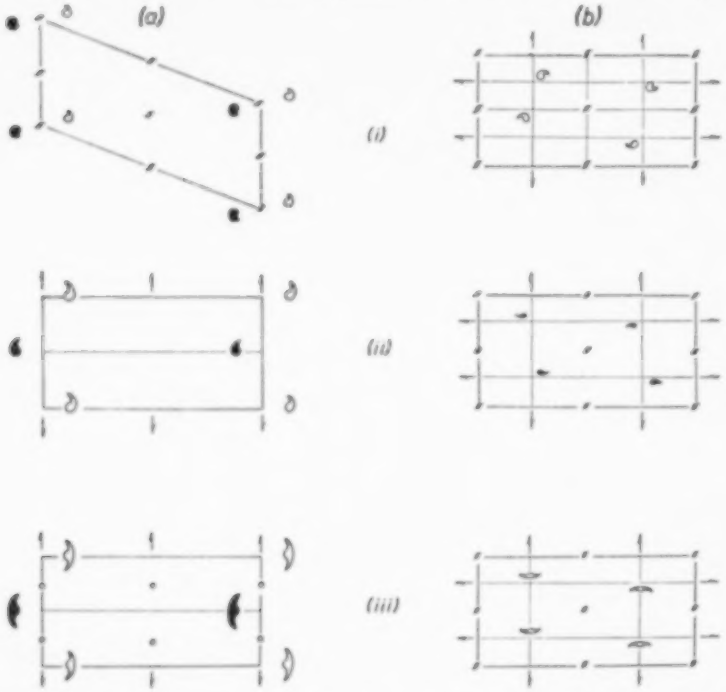

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Table 1. A list of the majority of natural product derivatives for which a detailed structure analysis is available, grouped according to the space group in which they crystallize

Compound	*Formula*	*No of Atoms*	*Cell dimensions*		*Space Group*
α-Bromocamphor[74]	$C_{10}H_{15}OBr$	11	7·38, 7·57, 9·12;	$\beta = 94°$	$P2_1$
Ephedrine hydrochloride[75]	$C_{10}H_{15}ON.HCl$	12	12·65, 6·09, 7·32;	$\beta = 102° 15'$	$P2_1$
Bromodilactone from jacobine[54]	$C_{10}H_{15}O_4Br$	14	9·11, 6·42, 10·84;	$\beta = 98·2°$	$P2_1$
Isoclovene hydrochloride[76]	$C_{15}H_{21}.HCl$	15	6·35, 13·91, 7·89;	$\beta = 95·3°$	$P2_1$
Ergine hydrobromide[77]	$C_{16}H_{17}ON_3.HBr$	20	9·60, 5·74, 13·79;	$\beta = 91·2°$	$P2_1$
α-Methodone hydrobromide[78]	$C_{21}H_{27}ON.HCl$	23	10·69, 8·74, 10·74;	$\beta = 94·6°$	$P2_1$
Thelepogine methiodide[80]	$C_{21}H_{34}ONI$	23	11·12, 13·04, 7·46;	$\beta = 109·5°$	$P2_1$
α-Methyldihydrothebaine methiodide[79]	$C_{21}H_{28}O_3NI$	25	11·06, 8·75, 10·54;	$\beta = 94° 32'$	$P2_1$
Calcium thymidylate[50]	$C_{10}H_{13}O_8N_2Ca.6H_2O$	26	14·40, 6·87, 9·81;	$\beta = 90·6°$	$P2_1$
7-Bromocholesteryl bromide[81]	$C_{27}H_{46}Br_2$	27	12·05, 8·75, 12·57;	$\beta = 101° 19'$	$P2_1$
Cholesteryl iodide[25]	$C_{27}H_{45}I$	27	12·57, 9·04, 21·89;	$\beta = 149°$	$P2_1$
Des-(oxymethylene)-lycoctonine hydroiodide hydrate[68]	$C_{24}H_{39}O_8N.HI.H_2O$	34	12·79, 9·44, 11·00;	$\beta = 97·75°$	$P2_1$
p-Bromobenzoate diester of iresin[52]	$C_{39}H_{39}O_6Br_2$	35	28·75, 7·41, 6·40;	$\beta = 92°$	$P2_1$
Phyllochlorine ester[53]	$C_{33}H_{38}N_4O_2$	39	12·23, 14·84, 7·87;	$\beta = 94° 59'$	$P2_1$
Lumisterol-4-iodo-3-nitrobenzoate[84]	$C_{35}H_{46}O_4NI$	40	10·55, 7·63, 20·57;	$\beta = 93·5°$	$P2_1$
Jacobine bromohydrin ethanolate[21]	$(C_{18}H_{26}O_6NBr)_2.C_2H_5OH$	53	10·11, 15·53, 14·90;	$\beta = 113°$	$P2_1$
Epilimonol iodoacetate[26]	$(C_{29}H_{21}O_8.COCH_2I)_2$	74	15·03, 12·36, 15·93;	$\beta = 95·2°$	$P2_1$
Quinine sulphate dihydrate[51]	$C_{20}H_{24}O_2N_2.H_2SO_4.2H_2O$	30	15·49, 6·74, 20·46;	$\beta = 114°$	C2
Strychnine sulphate pentahydrate[56]	$C_{21}H_{22}O_2N_2.H_2SO_4.5H_2O$	34	35·85, 7·56, 7·87;	$\beta = 107° 21'$	C2
Kojic acid[57]	$C_6H_6O_4$	9	3·85, 18·4, 8·55;	$\beta = 96°$	$P2_{1/n}$
Sodium tropolonate[58]	$C_7H_5O_2Na$	9	13·91, 3·69, 11·67;	$\beta = 93·1°$	$P2_{1/c}$
Tropine hydrobromide[59]	$C_8H_{16}ONBr$	10	6·32, 20·2, 7·44;	$\beta = 95°$	$P2_{1/n}$
Nootkatin copper complex[60]	$C_{30}H_{38}O_4Cu$	17	8·40, 11·96, 15·21;	$\beta = 115·5°$	$P2_{1/a}$
Cryptopleurine methiodide[55]	$C_{25}H_{30}O_2NI$	29	9·95, 24·2, 9·95;	$\beta = 112·0°$	$P2_{1/n}$

VOL
2
1961

ψ-Conhydrine hydrobromide[91]	$C_8H_{15}ONBr$	10	15·15, 9·28, 7·72	$P2_12_12_1$
Muscarine iodide[92]	$C_9H_{20}ONI$	11	6·81, 11·75, 15·40	$P2_12_12_1$
β-Biotin (vitamin H)[93]	$C_{10}H_{16}O_3N_2S$	15	5·17, 10·33, 21·00	$P2_12_12_1$
Hydroxydihydroeremophilone[7]	$C_{15}H_{24}O_2$	15	7·5, 10·0, 19·5	$P2_12_12_1$
β-Caryophyllene bromide[94]	$C_{15}H_{25}Br$	15	8·35, 10·75, 16·41	$P2_12_12_1$
Longifolene bromide[95]	$C_{15}H_{25}Br$	15	8·51, 9·78, 16·67	$P2_12_12_1$
Allokainic acid[51]	$C_{10}H_{15}O_4N$	15	26·08, 5·83, 6·95	$P2_12_12_1$
Kainic acid (Zn salt)[51]	$C_{10}H_{13}O_4NZn.2H_2O$	17	25·50, 6·93, 7·60	$P2_12_12_1$
Glutathione[96]	$C_{10}H_{17}O_6N_3S$	19	28·06, 8·80, 5·58	$P2_12_12_1$
Annotinine bromohydrin[39]	$C_{16}H_{22}O_3NBr$	20	11·89, 13·40, 9·68	$P2_12_12_1$
Benzyl penicillin (Rb salt)[53]	$C_{14}H_{17}O_4N_2SRb$	21	9·45, 6·44, 30·2	$P2_12_12_1$
Erythraline hydrobromide[41]	$C_{18}H_{19}O_3NBr$	22	13·36, 10·46, 11·67	$P2_12_12_1$
Morphine hydroiodide dihydrate[97]	$C_{17}H_{19}O_3N.HI.2H_2O$	23	20·32, 13·02, 6·84	$P2_12_12_1$
Gelsemine hydroiodide[24]	$C_{20}H_{22}O_2N_2.HI$	24	7·80, 9·17, 26·90	$P2_12_12_1$
Codeine hydrobromide dihydrate[98]	$C_{19}H_{21}O_3N.HBr.2H_2O$	24	13·10, 20·86, 6·82	$P2_12_12_1$
Himbacine hydrobromide hydrate[18]	$C_{22}H_{26}O_2NBr.H_2O$	26	12·67, 26·32, 6·68	$P2_12_12_1$
Aspidospermine-*N*(b) methiodide[48]	$C_{23}H_{33}O_2N_2I$	27	24·3, 8·5, 11·1	$P2_12_12_1$
Strychnine hydrobromide hydrate[38]	$C_{21}H_{22}O_2N_2.HBr.2H_2O$	27	7·64, 7·70, 32·2	$P2_12_12_1$
Calycanthine hydrobromide hydrate[50]	$C_{22}H_{28}N_4Br_2.2H_2O$	28	9·61, 14·13, 16·97	$P2_12_12_1$
Colchicine methylene bromide[99]	$C_{22}H_{25}O_6N.CH_2Br_2$	30	9·1, 14·87, 18·54	$P2_12_12_1$
Aureomycin hydrochloride[49]	$C_{22}H_{23}O_8N_2Cl.HCl$	32	11·20, 12·89, 15·47	$P2_12_12_1$
Lanostenyl iodoacetate[72]	$C_{32}H_{53}O_2I$	34	7·6, 10·9, 38·6	$P2_12_12_1$
Demethanol aconinone hydroiodide hydrate[40]	$C_{24}H_{35}O_4N.HI.3H_2O$	36	14·69, 22·08, 8·33	$P2_12_12_1$
Methyl oleanolate iodoacetate[100]	$C_{33}H_{51}O_4I$	37	7·7, 16·11, 25·14	$P2_12_12_1$
Calciferol-4-iodo-3-nitrobenzoate[46]	$C_{31}H_{20}O_4NI$	40	6·98, 15·3, 31·2	$P2_12_12_1$
Vitamin B_{12}[10]				
Vitamin B_{12} (wet)	$C_{62}H_{94}N_{14}O_{14}PCo.nH_2O$	105	25·33, 22·32, 15·92	$P2_12_12_1$
Vitamin B_{12} (dry)	$C_{62}H_{94}N_{14}O_{14}PCo.nH_2O$	103	24·35, 21·29, 16·02	$P2_12_12_1$
Vitamin B_{12}—ScCN	$C_{63}H_{94}N_{14}O_{14}PCoScCN.nH_2O$	99	23·98, 21·46, 16·02	$P2_12_12_1$
Vitamin B_{12} hexacarboxylic acid	$C_{49}H_{64}O_{14}N_5CoCl.2H_2O$	73	24·58, 15·52, 13·32	$P2_12_12_1$
Purpurogallin[101]	$C_{11}H_8O_5$	16	19·56, 24·6, 3·62	Pb2a
Bromoamphenicol[45]	$C_{11}H_{12}O_5N_2Br_2$	18	7·4, 17·9, 22·1	$C222_1$
α-Isosparteine hydrate[102]	$C_{15}H_{26}N_2.H_2O$	18	20·18, 10·61, 6·84	$C222_1$

reproduced by the symmetry element. In $P2_12_12_1$, there is a set of two-fold screw axes parallel to each of the three axes—an asymmetric unit is reproduced four times by the operation of the symmetry elements.

For $P2_12_12_1$ with a single heavy atom in the asymmetric unit, the heavy atoms can contribute to define the phase angle of almost all reflections with, however, the presumably rare possibility that they may lie in special positions, *e.g.* at a quarter position, *Figure 3* (*b*) (*iii*), where its effectiveness as a phase-fixing agent is compromised, as in the case of gelsemine hydroiodide[24]. On the other hand, for $P2_1$, if there is only one equivalent heavy atom, then it and its symmetry-related atom can be regarded as disposed around a centre of symmetry. We have noted earlier that, where a centre of symmetry is involved, the phase angles defined by the heavy atoms degenerate to either $0°$ or π. Hence, in this case, so far as the heavy atoms are concerned, the crystal structure is centrosymmetric and, if the heavy atom is used to initiate the analysis, it will impose this symmetry upon the diffraction data and thus upon the apparent structure. This situation is depicted in *Figure 3* (*a*) (*iii*) in contrast with the real situation in *Figure 3* (*a*) (*ii*). The situation may be described to a first, but necessarily crude, approximation by imputing half atoms on either side of the introduced reflection plane. For this situation, we therefore face a somewhat more intractable problem—the sites of the A_L atoms (if we recognize them) are now of half-weight except on the introduced planes of symmetry. Of the $2n$ sites, assuming that all are located sufficiently accurately and none are spurious, we have to distinguish which atoms are related to which to form a molecule. At this point, we must recognize that for this space group $P2_1$ with one heavy asymmetric atom we require to apply tests of chemical sensibility in terms of bond lengths and angles in the recognition of groups of stereochemical significance. The first complete analysis of a natural product—cholesteryl iodide by Carlisle and Crowfoot[25]—provides an excellent example of this dilemma. This situation does not apply to space group $P2_12_12_1$, at least in theory, although any chemical generalizations are useful guides at all stages of an analysis. However, for space group $P2_1$ they are a necessity. For such symmetrized structures, it is necessary to tilt the balance towards asymmetry in one direction or another by a conscious choice, *e.g.* in gelsemine hydroiodide[24], acceptance of the existence of the indole ring decided the balance in one direction and the remainder of the molecular skeleton was defined by gradually working outwards by iterative application of Fourier syntheses. Comparing the two space groups for an asymmetric unit of one molecule, the amount of diffraction data per molecule is the same, and hence, under comparable circumstances, it is more desirable to carry out an analysis with a structure crystallizing in $P2_12_12_1$, since ambiguities are less likely to arise. For this reason also, the comparative numbers of structures in $P2_1$ and $P2_12_12_1$ which have been analysed (see *Table 1*), may have no statistical significance in terms of their distribution in Nature, but rather are representative of the relative difficulties of analyses with the respective space groups.

For $P2_1$, the ambiguity arising from the existence of one heavy atom in the asymmetric unit may theoretically be eliminated by introducing a second heavy atom. This situation was found to exist in the case of the iodoacetate of epiliminol[26], which crystallized with two molecules in the

VOL. 2 1961

asymmetric unit, the two iodine atoms being at different y levels. However, such a situation may well lead to further complication as was found for jacobine bromohydrin[21]. Here also there were two molecules in the asymmetric unit, but the situation was degenerate since both Br atoms were on the same y level.

Vector distribution

With the experimental data, one more step may be carried through without assumptions other than those involved in the well-defined operations of the space group. Because the crystal is periodic in three dimensions, we may convert our data in diffraction space into an equivalent distribution in real space by means of a Fourier synthesis whose terms are $|F|^2$. Since $|F|^2 = F.F^*$, this calculation (3) required no information regarding phase:

$$P(XYZ) = \frac{1}{V_c} \cdot \sum h \sum_{-\infty}^{+\infty} k \sum l \left|F(hkl)\right|^2 \cos 2\pi(hX + kY + lZ) \qquad (3)$$

Patterson[23], who introduced this function in 1935, showed that it gives not atomic positions but the array of vectors between every pair of atoms, all the vectors starting from the origin of the unit cell. Thus, if there are N atoms in the unit cell, there are $N^2 - N$ vectors in the distribution P. If N is 100 (say), then there are 9900 vectors. However, this complication is unavoidable in transferring to real space without information regarding phase angles. At the least, the vector distribution is equivalent to the data in diffraction space, and is more readily comprehensible in terms of bond lengths and angles and the general stereochemistry of molecules.

Methods of analysis

We may now consider the steps by which the complete molecular structure can be extracted from the diffraction data.

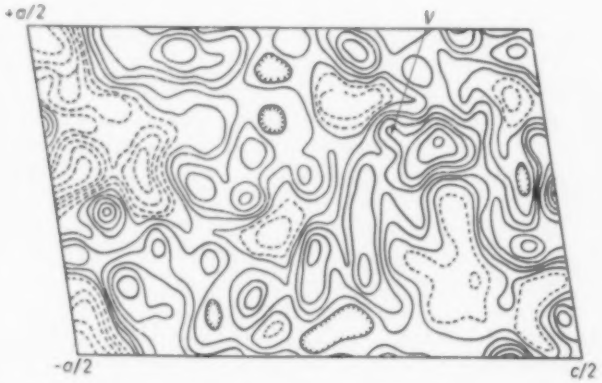

Figure 4. A contoured vector map showing the location of the vector peak, *V*, between two S atoms. The vector peak is not immediately obvious and internal evidence was required to reveal its significance

The first step is to determine the peaks corresponding to the A_H–A_H vectors in the vector distribution. These may be immediately obvious; but, if the A_H atoms are of inadequate weight, then tests involving internal consistency of the vector distribution may be required to distinguish the true A_H–A_H vector peak from peaks of comparable size, due to coincidence of several minor vectors, *e.g.* in tosyl-prolyl-hydroxyproline[9] (*Figure 4*) and in cephalosporin C[27]. Confirmation of the correct selection is particularly necessary where there are several atoms of only moderate weight; *e.g.* in the carbon tetrachloride adduct of sporidesmin[28] there are seven A_H atoms to locate, two S and five Cl. However, we shall assume that the A_H–A_H vectors can be identified and that, from their location, the sites of the A_H atoms in the unit cell can be deduced.

This is the basic information to be used to locate the lighter atoms, so that they may be grouped to form the molecular skeleton(s) and the atoms differentiated into C, N and O.

If the analysis is started from an empirical formula, we must have no preconceived ideas regarding the molecular shape. In the early stages, it will not be possible even to tell which regions in the unit cell enclose the molecule(s), particularly if there is more than one molecule in the asymmetric unit. It is important not to superimpose one's ideas upon the data, since it is found in practice that it is extremely easy with asymmetric structures to persuade the data in the direction we wish it to go. This arises from the flexibility of definition of the phase angles and the large numbers of parameters involved in this type of analysis. This has been especially noted in the analysis of the vitamin B_{12} group of compounds by Hodgkin and her co-workers[19, 20, 29] and we have had similar experience with jacobine bromohydrin[21] and thelepogine methiodide[30].

For this reason, it is important to handle the diffraction data so that the derived information should have maximum structural significance, a minimum of spurious detail, and lead to the correct solution in a minimum number of stages. If one deviates from the right track, it will be possible to correct the error because of the inherent properties of the Fourier method, but this may require time-consuming cycles of calculation to resolve the dilemma. Since the data initially in the form of a vector distribution will be eventually unravelled, and the molecular structure presented more clearly in the form of the electron density distribution, the various approaches to the process of structure analysis by this method may be differentiated by the point at which the transfer from the vector map to the direct ρ map occurs. As we have noted previously, the vector distribution contains all the structure information with the minimum of assumption, and accordingly it appears advisable to use this function to extract as much structural information as possible before transferring to the electron density representation.

Although the vector distribution was proposed by Patterson in 1935[23], a systematic method of extracting information was not developed until 1950, when Buerger[31] presented his image-seeking approach based on an earlier suggestion by Wrinch[32]. Other approaches of a similar type were proposed almost simultaneously by Beevers and Robertson[33], Clastre and Gay[34] and Garrido[35]. These processes consist of placing in the vector distribution a search-polygon which may represent a part or whole of a molecule, com-

VOL. 2 1961

bining the values at the vertices of the polygon (*i.e.* at atom centres) and transferring the combined values to form one value in a new derived distribution. The polygon (or molecule) is moved over all possible positions, keeping the orientation fixed, and the complete new distribution is derived. There is a variety of methods of combining the values, but, in practice, since we are dealing with a complex situation, the individual operations must be uncomplicated and capable of rapid exploitation. The only ones which have proved satisfactory in use are the simple summation and the minimum function. We can see that if the search-polygon coincides with a number of high peaks in the vector map, a high peak is reproduced in the new distribution and this result will be structurally significant. Theoretically, one can start with only two atoms as search points and, as new atom sites are revealed, these are added to the search-polygon until finally the whole molecule is involved and the derived function shows only what was put in—with no spurious features. In practice, as is usual, many problems obtrude upon this idealized scheme, some of which are dealt with in Buerger's book *Vector Space*[36].

However, all operations are carried out on the vector function, and so the image-seeking approach is in accord with our premise. The process of

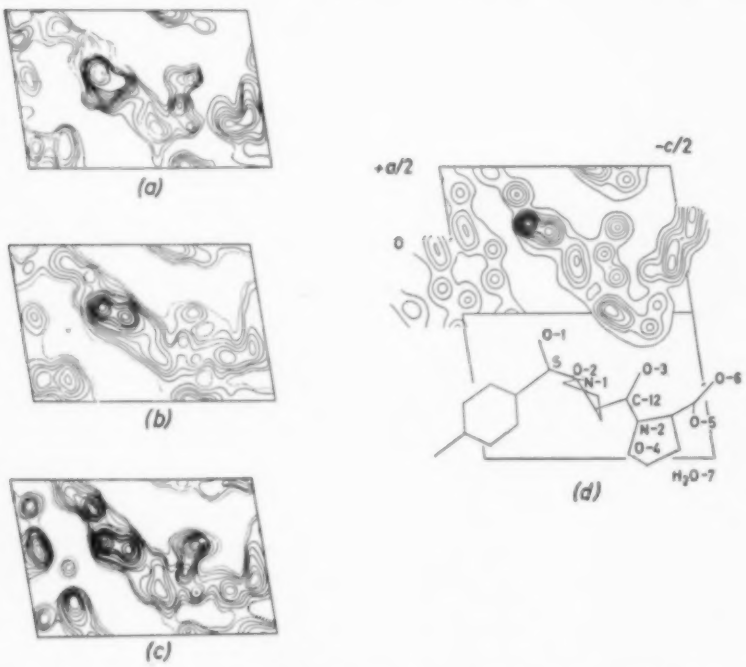

Figure 5. Image-seeking by calculation of Fourier syntheses using terms $|F_o|^2 \times \phi_c$. ϕ_c corresponds in: (*a*) to S; (*b*) to S + (N–1 + O–2); (*c*) to S + (N–1 + O–2) + the tolyl ring + O–1 + O–3 + C–12. The improvement with increasing number of atoms in the search-polygon is shown by comparison of (*a*), (*b*) and (*c*) with (*d*), the final electron-density distribution. The distribution (*c*) is calculated on the basis of knowledge of the location of approximately half the total number of atoms in the molecule

image-seeking may be carried out by inspection, somewhat more exactly by hand calculation and most expediently by an electronic computer. Alternatively, the combination of the vector distribution by summation may be replaced exactly and often more conveniently by a Fourier synthesis with terms $|F(hkl)|^2 \times \phi_e$ [37], where ϕ_e is the structure factor of the search-polygon. An illustration of this latter process is given in *Figure 5*, which shows the influence of increasing the number of atoms in the search-polygon. The final electron-density map is shown for comparison.

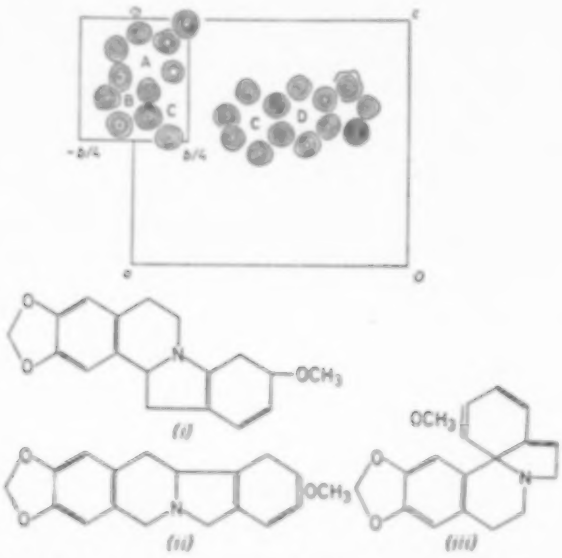

Figure 6. Part of the final three-dimensional electron-density distribution of erythraline hydrobromide. The group of atoms on the left forming rings A and B must be visualized as rotated 90° to join with the atomic group on the right through ring C. (*i*), (*ii*) and (*iii*) were possible structural formulae on the basis of chemical evidence

With regard to natural products, this method was first developed and applied in the analysis of strychnine hydrobromide by Beevers and Robertson[38] in 1950. Subsequently, Przybylska has made use of image-seeking by inspection in the analysis of annotinine bromohydrin[39] and demethanol aconinone hydroiodide[40]. The best example, using the $F^2 \times \phi_e$ method, has been by Nowacki and Bonsma in their analysis of erythraline hydrobromide[41]. Here the structure was derived almost completely from the first image-seeking operation. Part of the final result is shown in *Figure 6*, the three-dimensional array of atoms being in accord with structural proposals of Prelog and co-workers. The minimum image-seeking function has been less widely used in this field of natural products, a notable exception being the analysis of cellobiose[42] by Lipscomb and co-workers.

Before a systematic treatment of the vector distribution had evolved, the usual method of analysis was to discard the Patterson function as soon as the heavy atoms had been located, and to use the direct representation of

VOL. 2 1961

the electron density. At first, the representation would only approximate crudely to the " true " distribution, since phase angles were defined by the heavy atoms alone; but as single atoms or groups of atoms were recognized, their contribution to the phase angle was incorporated, and the cycle of structure factor and electron-density calculation repeated until the conditions for a satisfactory analysis were achieved, *i.e.* all peaks structurally significant used in (1) and (2)*. For this approach, the classical work

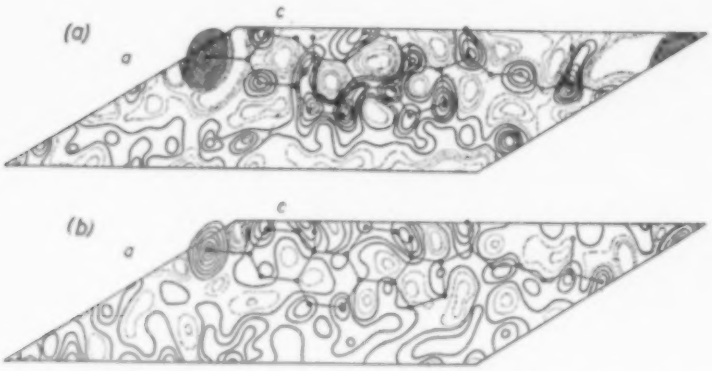

Figure 7. Cholesteryl iodide B. Two sections of the three-dimensional distribution of electron-density (*a*) at $y = 0{\cdot}25$, and (*b*) at $y = 0{\cdot}33$

which established the value of the heavy atom method as yielding the molecular structure without assumptions was the analysis of Pt phthalocyanine by Robertson and Woodward[44], while the first significant application to natural products was the analysis of cholesteryl iodide by Carlisle and Crowfoot[25] (see *Figure 7*). A striking example of the application of this method was given by Dunitz in 1952. Despite rather difficult experimental conditions—decomposition of the crystal to a gum under X-radiation—an analysis of bromoamphenicol[45] was completed. In this, Dunitz succeeded in showing that the first three-dimensional electron density distribution, based on the Br atoms, yielded the three-dimensional atomic array of the molecular skeleton (see *Figure 8*).

The most extensive application of the use of the direct distribution† is in the analyses of the group of vitamin B_{12} compounds—wet and dry vitamin B_{12}, vitamin B_{12}—SeCN and the derived hexacarboxylic acid by Hodgkin and her co-workers[19]. Perusal of the work already reported[19, 20, 29], describing an outline of the investigation of vitamin B_{12} and the crystal structure of the hexacarboxylic acid (see *Figure 9*), will give a greater appreciation of the process of approximation to the complete and correct

* To speed up the derivation of the complete structure, Sim[43] has proposed the weighting of individual $|F|$ terms by a function representing the probability of the phase angle being correct. This scheme was used in the analysis of epiliminol iodoacetate[28].

† By single-derivative single-crystal techniques, to differentiate from the multi-derivative single-crystal methods of Perutz and co-workers and Kendrew and co-workers in their analyses of haemoglobin and myoglobin respectively.

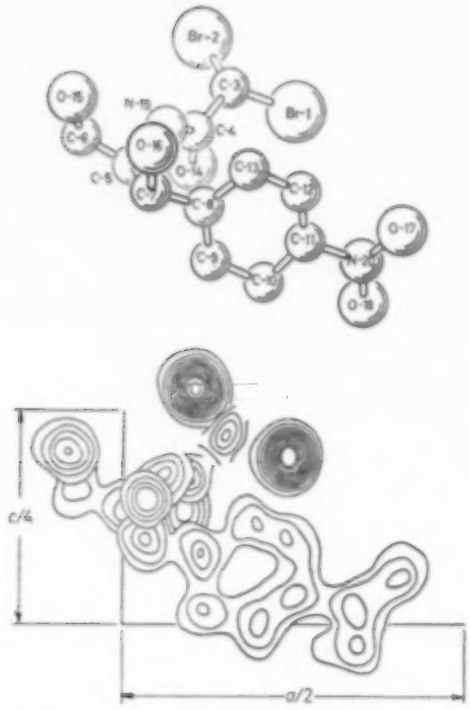

Figure 8. Sections of the three-dimensional electron-density distribution of bromoamphenicol from which the atomic array, shown above, was deduced

structure. For the hexacarboxylic acid, an idea of the magnitude of the calculations involved may be suggested by the observation that there are 73 atoms in the molecule and ten three-dimensional electron density distributions were computed[20]. The story of this group of compounds is not yet complete, but it is already so extensive that it would be invidious to deal with it here. There would be little time left for the smaller molecules on which I have preferred to focus attention.

At this point we may note that, where a considerable part of the molecule is known, the process of analysis is much more rapid in achieving a final answer, *e.g.* in the case of calciferol[46], which required only two cycles of three-dimensional calculation.

In the more recent analyses of natural products, *e.g.* those of iresin[47], aspidospermine[48], gelsemine[24], aureomycin[49], calycanthine[50], and kainic and allokainic acids[51], the use of the electron-density distribution as soon as the heavy atoms have been located has proved more popular than image-seeking methods. These analyses have usually involved quite a number of cycles of calculation to arrive at the final answer. It would, however, appear to be profitable to make a careful comparison of this method with that of the image-seeking methods, in particular to consider whether a combination

VOL. 2 1961

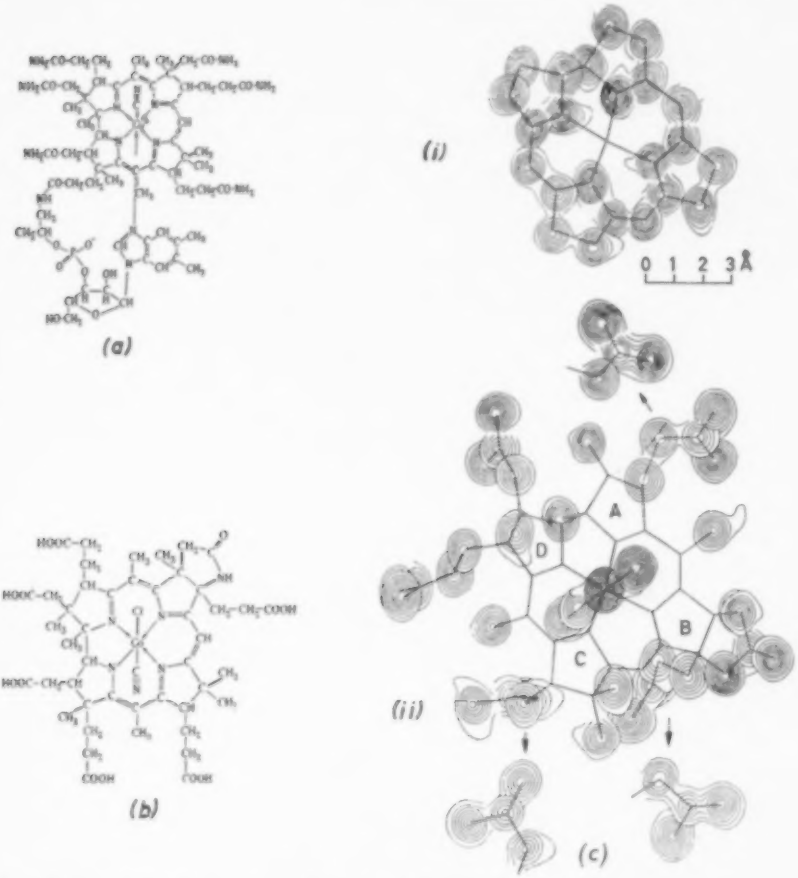

Figure 9. The molecular structures of (*a*) vitamin B_{12} and (*b*) the hexacarboxylic acid derived from vitamin B_{12}, as deduced from X-ray data; and the three-dimensional structure (*c*) of the hexacarboxylic acid, the atoms being indicated by contour sections near the atom sites. For clarity, the contoured distribution is shown in two parts: (*i*) the corrin nucleus; and (*ii*) the remainder of the molecule. Where atoms overlap in this projected view, groupings of sections at right angles are displayed adjacently

of such methods would approach the correct result more rapidly. We may note that, in the analysis of strychnine hydrobromide[38], an electron density map was used as a check on the results of the image-seeking procedure, while for epilimonol iodoacetate[26], an image-seeking function by direct superposition was used as a check on the first electron-density distribution. In the analysis of jacobine bromohydrin[21] (a rather severe test-case due to the presence of two molecules in the asymmetric unit and the coincidence in *y* levels of the Br atoms), we first used three-dimensional image-seeking by calculation[37]; but we were dissatisfied with the apparent large amount of spurious detail, so an electron-density distribution was calculated with a

high cut-off, *i.e.* only terms for which the Br atoms contributed 45 per cent or more of their maximum value were used. It was found that minor details were not coincident in the two distributions. Hence coincidences of positive peaks in both could be taken as structurally significant, and on this basis it was possible to extract 52 atoms which grouped into two chemically sensible molecules (identical to a first order)*. The resultant grouping of the molecules of jacobine bromohydrin is shown in *Figure 10*. The structure amplitude comparison for the 55 atoms in the asymmetric unit are grouped in *Table 2*. The data are grouped for constant k. The good agreement at

Table 2. The measurement of agreement, R, between the experimental values of $|F|$, including " unobserved " terms, and those calculated for the first set of sites for the 55 atoms derived from the combined use of image-seeking and an electron-density distribution with high cut-off

k	$\Sigma\|F_o\|$	$\Sigma\|F_c\|$	$\Sigma\|\Delta F\|$	R*
0	10,588·7	10,241·0	2,177·5	$0{\cdot}20_6$
1	11,375·8	10,588·0	2,089·1	$0{\cdot}18_4$
2	10,661·6	10,159·8	2,066·2	$0{\cdot}19_4$
3	9,394·0	9,925·0	2,065·6	$0{\cdot}22_0$
4	8,793·4	9,278·3	2,337·2	$0{\cdot}26_6$
5	8,615·8	8,874·4	2,405·7	$0{\cdot}27_9$
6	7,815·5	8,274·4	2,387·1	$0{\cdot}30_5$
7	7,756·2	7,660·8	2,721·1	$0{\cdot}35_1$
8	7,235·1	7,220·6	2,662·5	$0{\cdot}36_8$
9	6,124·6	6,435·7	2,437·2	$0{\cdot}39_8$
10	5,662·6	5,723·7	2,456·4	$0{\cdot}43_4$
Σk	94,024·3	94,381·7	25,805·6	$0{\cdot}27_4$

* $R = \Sigma|\Delta F| / \Sigma|F_o|$, where $|\Delta F| = |F_o| - |F_c|$

low k is indicative of the general correctness of the molecular structure, while the steady trend of R with increasing k suggests that displacement of atoms is required in the y direction, individually or a molecule as a whole. The structure arrived at is in agreement with the formulation proposed by Geissman[52], but gives in addition full details regarding conformation and configuration.

We have dealt mainly with three-dimensional methods of analysis, since these represent full use of the data, lead to a less equivocal result and are perfectly possible if one has easy access to a large-scale computer. There are, however, occasions when, for reasons of computer distance or economy, it may be advantageous to use two-dimensional or partial three-dimensional data. The diffraction data for each layer may be dealt with separately in the form of normal or generalized projections†. The normal projection has considerable restrictions for work on natural products (*e.g.* the analysis

* Although two molecules per asymmetric unit are a disadvantage to an analysis at an early stage, they provide useful supporting evidence of internal consistency during the later stages (see also epiliminol[26]).

† This does not contradict the statement made earlier in the text, as the data are not used piecemeal but in specific related groups (layers).

VOL. 2 1961

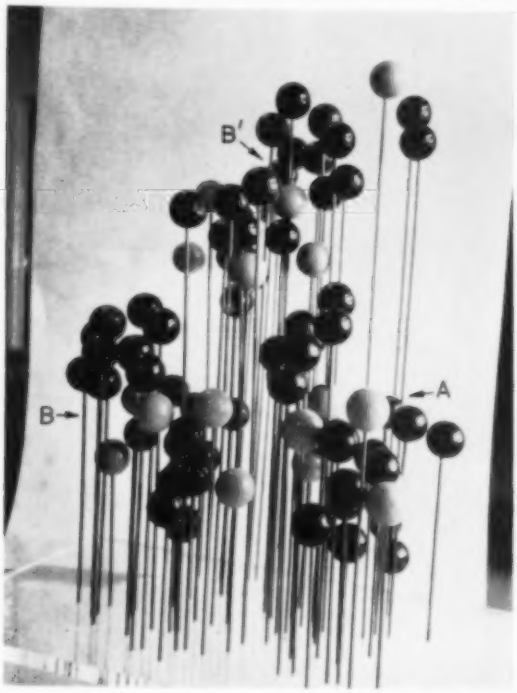

Figure 10. Grouping of molecules in the crystal structure of jacobine bromohydrin ethanol adduct. Molecules A and B are not related by symmetry; B and B′ are crystallographically related by a diad screw axis

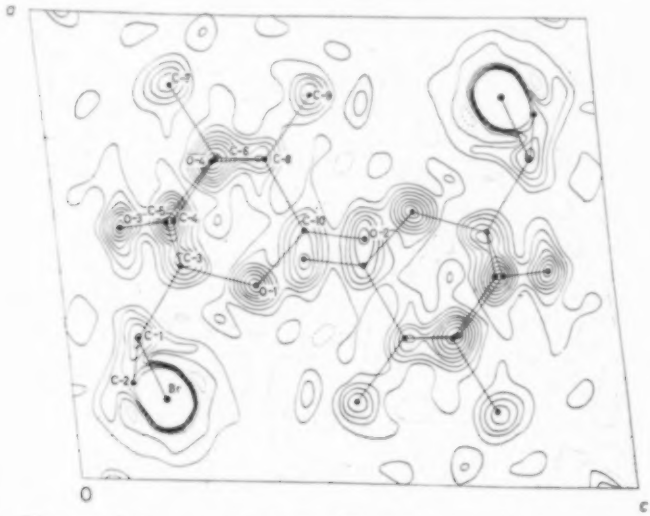

Figure 11. The crystal structure of the bromodilactone from jacobine. Projection of the electron-density distribution down the *b* axis with line diagrams of the two symmetry-related molecules superimposed

of benzyl penicillin[53], which was mainly two-dimensional in the early stages), but it may still be of assistance for smaller molecules. A case in point is that of the bromodilactone from jacobine[54] (see *Figure 11*), the structure analysis of which provides further corroborative evidence of the correctness of Geissman's deductions regarding this group of alkaloids from *Senecio jacobaea* L.[52]. For normal projections, the x,y parameters are determined by the position of the peak while, for the corresponding generalized

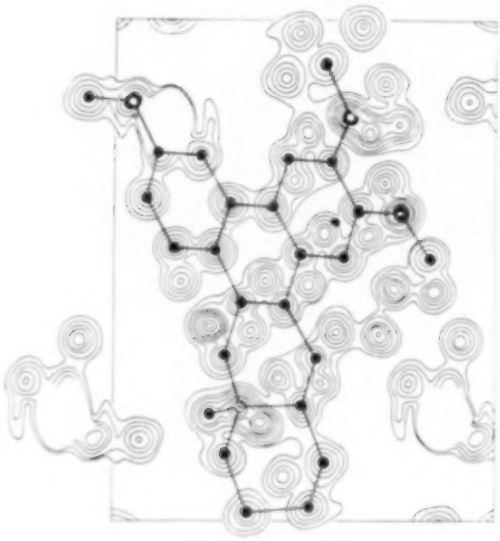

Figure 12. A combination of the normal projection and modulus projections for first- and fifth-layer data to produce clear resolution of the atoms. A line diagram of one molecule ((±)-cryptopleurine methiodide) is superimposed

projections, the third parameter z is derived from the magnitude and sign of the peak value in the cosine and sine components. Because these latter distributions are two-dimensional in essentials, they can be handled more rapidly than three-dimensional distributions while it is possible to combine the two components, C_l and S_l, of any layer to yield $|\rho_l| = (C^2_l + S^2_l)^{\frac{1}{2}}$, a modulus projection which, with certain reservations, should be the same as the normal ρ_0 projection. Use was made of this property of modulus projections* in the analysis of (±)-cryptopleurine methiodide[55], an interesting example since the structure first determined by X-rays (see *Figure 12*) was later confirmed by chemical synthesis by two independent groups[56, 57]. Use has been made of generalized projections in the determination of the configuration of the α-prodine molecule by Ahmed, Barnes and Kartha[58],

* The distribution of spurious detail in ρ_0 and any $|\rho_l|$ does not coincide, since both are derived from different sets of data. As a result, it is possible to extract the coincident peaks as significant structurally.

VOL. 2 1961

while we have utilized both generalized and modulus projections in the analysis of himbacine hydrobromide[18] (see *Figure 13*) and thelepogine methiodide[73].

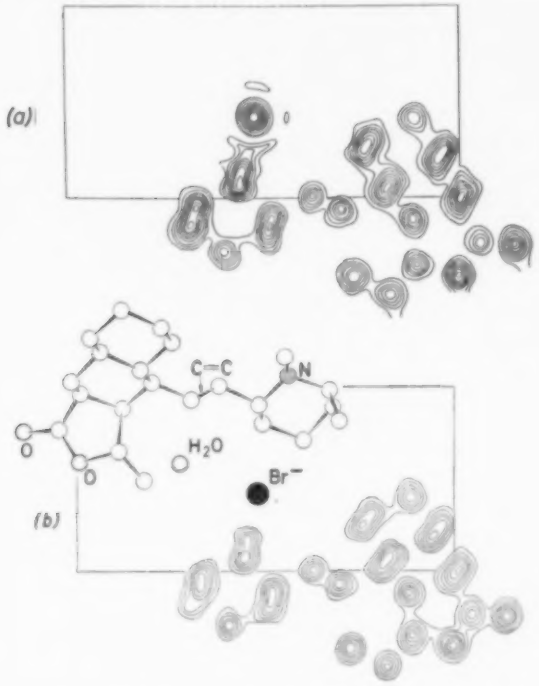

Figure 13. A comparison of (*a*) the normal projection and (*b*) the modulus projection from first-layer data for himbacine hydrobromide. The absolute configuration of the molecular skeleton is shown in (*b*)

One invaluable technique which is auxiliary to all the methods discussed above is the difference method, developed and systematized by Cochran[59]. The difference between the distributions based on F_o terms and on F_c terms is calculated by equation (5):

$$\Delta\rho = \rho_o - \rho_c = \frac{1}{V_c}\sum h \sum_{-\infty}^{+\infty} k \sum l \,(F_o(hkl) - F_c(hkl))$$
$$\exp\left\{-2\pi i(hX + kY + lZ)\right\} \quad (5)$$

In this new function, errors and discrepancies in the calculation of structure amplitudes are accentuated, and can be identified and corrected. It has been used to determine the asymmetric vibrations of atoms and molecules and to reveal errors in scattering curves. For our purposes, it can be used: (1) to differentiate light atoms, *i.e.* C, N and O; (2) to refine atom positions; and (3), most important, to assist in the location of lost or wrongly-placed

atoms. The method, under the name " error synthesis ", was used by Bunn and Turner-Jones during the analysis of benzyl penicillin[53]. Two examples of the application of difference methods in a complex structure are shown in *Figure 14*.

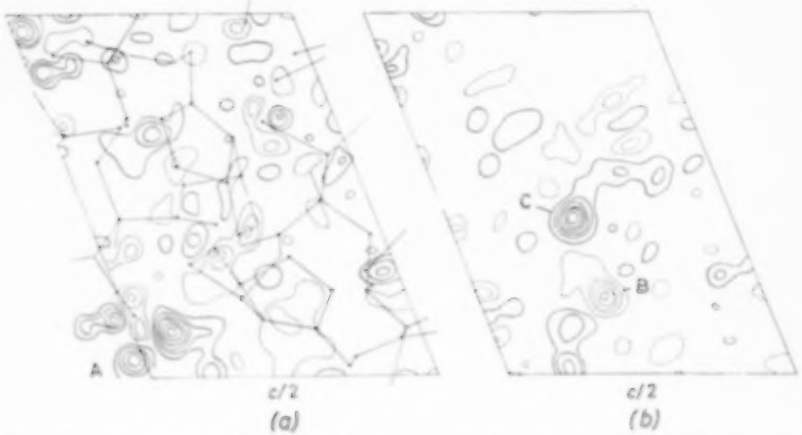

Figure 14. Applications of " error " or difference methods in locating atoms and correcting wrongly-placed atoms. (*a*) Contoured difference map of a zero-layer projection after the 52 atoms constituting the two molecules of jacobine have been subtracted. The ethanol molecule is revealed by the contoured positive region, A. The projection is down 15·5 Å. (*b*) Contoured difference map after the 55 atoms of the asymmetric unit were subtracted. In calculating the structure factors, the z parameter of one atom was misread as 0·219 instead of 0·421$_5$. The difference map reveals this slip by the negative (dashed) region at 0·219, B, and a positive region at 0·422, C, to which the atom site had to be shifted. Despite the fact that 55 atoms are involved, these two complementary features dominate the distribution

The most striking use of difference methods has, however, been to show the location of hydrogen atoms, *e.g.* as shown in *Figure 15*[60]. This requires fairly accurate intensity data, and is not indicative of the normal analysis of a natural product. For definite location of hydrogen, other techniques, *e.g.* N.M.R., are more rapid once the skeleton has been defined. However, we must note that, if the X-ray analysis has been carried out with data of adequate accuracy and range and has been refined sufficiently, so that atom positions are accurately fixed, then it will be possible to place the hydrogen atoms on the basis of the stereochemistry of the molecule.

The determination of absolute configuration

So far we have been concerned with the derivation of the structure of the molecule from which details of conformation and the relative configuration can be defined. The final step, the determination of the absolute configuration, is a relatively minor step experimentally, but it has taken a rather long time to arrive at what is now obvious—a fairly persistent pattern in research. In 1930, Koster, Knol and Prins[61] showed experimentally that, using X-radiation whose wavelength was just short of the absorption edge for Zn, it was possible to distinguish the Zn side from the S side of the ZnS layer structure by the breakdown in Friedel's law, $F^2(hkl) = F^2(\overline{hkl})$.

It was, therefore, possible to establish the absolute orientation of any ZnS crystal or any other crystal of similar type. Twenty-one years passed before the significance of this observation for organic chemistry was recognized by Bijvoet, who put the idea to the test in a classical experiment with NaRb tartrate and ZrK α-radiation[62]. It was later shown by Peterson[63] (in Bijvoet's group) that, although careful choice of radiation with respect to the anomalous scatterer accentuated the effect, it is possible to measure

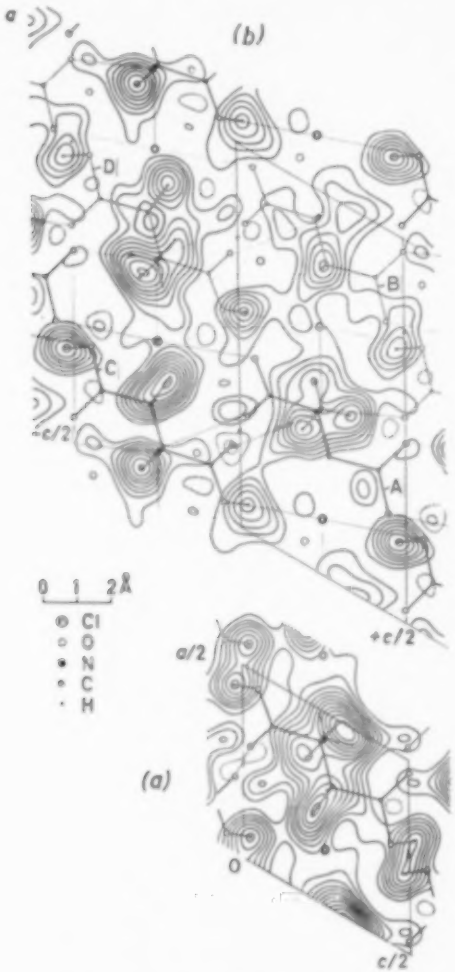

Figure 15. The application of difference methods in the location of hydrogen atoms. The crystal structure is (±)-aspartic acid hydrochloride. (*a*) The zero-layer difference map from which the aspartic acid skeleton and the Cl^- ion have been subtracted, leaving the distribution corresponding to the hydrogen atoms. (*b*) A combination of the zero-layer and first-layer cosine and sine generalized difference maps to pick out the hydrogen atoms at different levels of the third (*y*) dimension. Line diagrams of the four molecular skeletons in the unit cell, which have been subtracted, are superimposed

the differences in intensity even when the heavy atom absorption edge lies a considerable way from the wavelength of the radiation used. This observation enabled the technique to be applied without special experimental conditions. Thus, it was shown that it was possible to define the absolute configuration of strychnine hydrobromide[64] using Cu radiation. We have used this technique to define the absolute configuration of himbacine hydrobromide[18] and jacobine bromohydrin[21].

For a heavy atom such as I with Cu radiation, the effect of anomalous dispersion is more marked than for Br, since $f'' = +7{\cdot}2$ for CuK radiation ($f = f_0 + f' + if''$, where $f_0 = 53{\cdot}0$). This is reflected in the larger differences in intensity, often readily visible to the eye; and, under such conditions, Przybylska and Marion have defined the absolute configuration[65] of (+)-des-(oxymethylene)-lycoctonine hydroiodide[66] and (+)-demethanol-aconionone hydrioiodide[60] (see *Figure 16*).

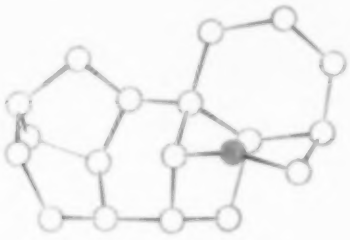

Figure 16. The absolute configuration of the molecular skeleton common to des-(oxymethylene)-lycoctonine and demethanolaconinone

Although of lesser interest, an alternative method more akin to the chemical approach is the introduction of a known absolute centre with the heavy atom[67]. With this technique, the analysis proceeds normally and the final structure contains its own reference standard. An example is the analysis of (+)-*S*-methyl-L-cysteine-*S*-oxide[68]. The analysis of vitamin B_{12} illustrates both methods, since the absolute configuration of the molecule in the earlier stages of the analysis was defined by reference to the D-ribose component[19], while later this decision was confirmed by reference to the anomalous dispersion of the Co atom in the hexacarboxylic acid[20].

The definitive experiment of Bijvoet and his co-workers and its implications have already had considerable influence on the definition of configuration in organic chemistry, and have evoked a new set of rules by Cahn, Ingold and Prelog[69] to overcome inconsistencies in nomenclature.

That the anomalous dispersion effect may be of greater significance than the definition of configuration, that it may be of direct use in structure analysis, was realized early. However, since the intensity differences are small, the necessity for very accurate intensity measurement is one which has not yet been made completely practicable for complex molecules. Peterson[63] illustrated its feasibility and Srinivasan[70] has applied it to an analysis of L-tyrosine. Okaya, Saito and Pepinsky[71] have suggested a neat method of unravelling the vector distribution by this technique (see also Pepinsky[5]).

It is clearly a technique with great possibilities, but the experimental problems of very accurate intensity measurements for a large number of reflections remain, a point which was made earlier.

CONCLUSION

I have attempted to indicate the peculiar advantages of this technique in the natural product field, in that it is not dependent on a mass of associated chemical evidence but is based on a few well-founded principles. Thus it would appear that the rôle of the X-ray diffraction method may lie, not in confirming fairly well-defined or worked-over structures, but rather in entering the field at an early stage—before the bone has been well chewed—and deriving the structure rapidly. To have on hand even partial chemical

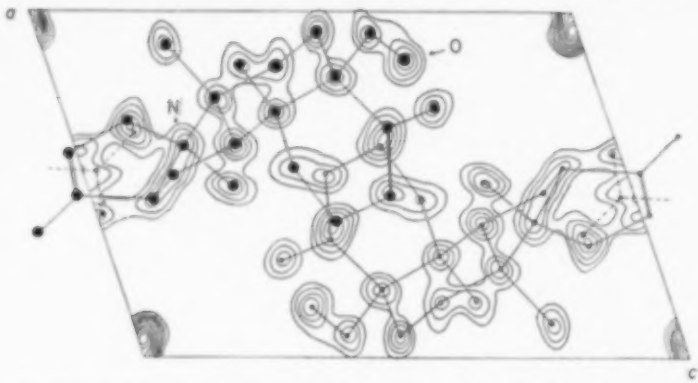

Figure 17. The molecular structure of thelepogine methiodide determined by X-rays. The electron-density distribution projected down the *b* axis (13·0 Å) is shown with line diagrams of the two symmetry-related molecular skeletons superimposed. The N and O atoms are indicated and the double bonds deduced from the detailed stereochemistry marked in the line diagram

information may give false confidence in steps and decisions which may later be found invalid—they will be corrected, but with expenditure of time and effort. It has appeared to us important to show that it is possible to work without supporting information. This was the main theme in our earlier work on lanostenol[72] and cryptopleurine[55], but in the analysis which we have just completed we have come nearest to the ideal conditions which we postulated. I will not give much detail, as these are to be given later, but indicate only the starting point and the end result.

The alkaloid thelepogine[73], from a grass, was available only in very small amount. A microanalysis of the alkaloid and of its methiodide (now regarded as $C_{21}H_{34}ONI$) were available, together with an estimation indicating only one C—CH_3 group. The X-ray analysis of the methiodide was begun towards the end of last year, and the result so far is shown in *Figure 17*. The molecular skeleton has been located, the N and O differentiated and the bond lengths and angles sufficiently well-defined to determine the location of double-bonds and the most probable disposition of the hydrogen atoms. Not only are the configurations of the six asymmetric

centres in the molecule placed on a relative basis, but the absolute configuration shown in *Figure 17* has been defined by the use of the anomalous dispersion of the I atom to the CuK_α radiation used in the analysis. One point which was unexpected and may be of chemical interest is the existence within the molecular skeleton of a pyrrolizidine ring system which has the same absolute configuration as found in jacobine bromohydrin.

The deduction from the evidence which we have presented is that, in the range of molecules up to 100 atoms (excluding H), and probably beyond, the structure can be solved in a time which compares favourably with other physical methods, provided that certain preliminary conditions are satisfied and a computer of reasonable storage and speed is available. Nor need this work necessarily involve a large team—the three analyses, of himbacine hydrobromide[18], jacobine bromohydrin[21] and thelepogine methiodide[30], some details of which I have used to illustrate various points, were initiated and solved in a period of less than two years. Because of the mass of detail required for an analysis and the extensive data derived from the work, however, it is important to use this technique for compounds either of great significance in themselves or those which provide a structural key to a group of compounds.

I wish to express grateful thanks to my colleague, Mr J. Fridrichsons, for his collaboration and unflagging support in the work which has formed the basis of opinions expressed here; to Drs J. R. Price, W. D. Crow and C. C. J. Culvenor of Melbourne, and Drs E. Ritchie and W. C. Taylor of Sydney, for, without their willing and generous co-operation (a) in allowing us to tackle problems which they might well have desire to retain for their personal study, and (b) in providing excellent crystals of the derivatives, we would not have had such interesting compounds to work on; and finally, to the invaluable co-operation of the respective staffs of the electronic computers SILLIAC (University of Sydney) and UTECOM (University of New South Wales).

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VOL. 2 1961

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VOL.
2
1961

TERPENIC COMPOUNDS WITH MEDIUM-SIZED RINGS

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The study of all aspects of living matter is a constant source of information and stimulation of the greatest theoretical and practical importance. The very origins of organic chemistry are rooted in a desire for knowledge of the composition of living bodies and the products of their metabolism, and, ever since the birth of our science, the study of natural products has always remained one of its important concerns. The investigation of plant constituents has been of particular significance for the development of organic chemistry; it should be borne in mind that the plant kingdom accounts for much the greatest part of living matter on our earth—more than 99·9 per cent, in fact! Moreover, plants not only produce all the types of compounds found in the animal kingdom but also a number of special groups of organic substances, especially terpenoids, alkaloids, and glycosides. The varied chemical structure of the numerous, genetically related compounds of these groups, and the biological activity and practical importance of many of them have ever invited their closer investigation, and it may be said fairly that the systematic researches in these fields have contributed greatly to the finest traditions of organic chemistry, and to the present extent and variety of this science.

In my opinion, it is the work on terpenes and steroids which was of the greatest importance in the development and shaping of organic chemistry. On the one hand, there is the classical unity of each of these groups, given by their simple composition, limited to the three basic organogenic elements, and by the uniformity of rules governing their structure; on the other hand, we have the great structural diversity and ubiquity of occurrence—it is these features which have made the terpene and steroid field an arena in which many minds active in our science have tried their strength. It was in research on substances of these two groups that the principal methods of structural analysis of organic compounds were devised and put to the test, especially the methods of controlled degradation; at the same time, it provided a powerful stimulus to the development of synthetic methods. Studies on the alicyclic terpenes, and on the whole steroid group, have been the source of our present ideas on the spatial structure of organic compounds. The whole of chemistry has profited from the valuable techniques developed in these fields for the isolation of individual substances from complex mixtures, their characterization and identification by physical constants. Let me recall particularly the determination of relations between chemical structure and physical properties, especially spectroscopic properties, which form such an essential part of organic chemistry today.

I must confess to a great love for these two groups of natural substances. In today's talk I should like to review for you some results from the chemistry of the sesquiterpenes—a group of terpenoids which has only been studied in detail rather recently. Today, we know this group to be varied and rich in structural types; this is clearly illustrated by *Figure 1*, which shows the

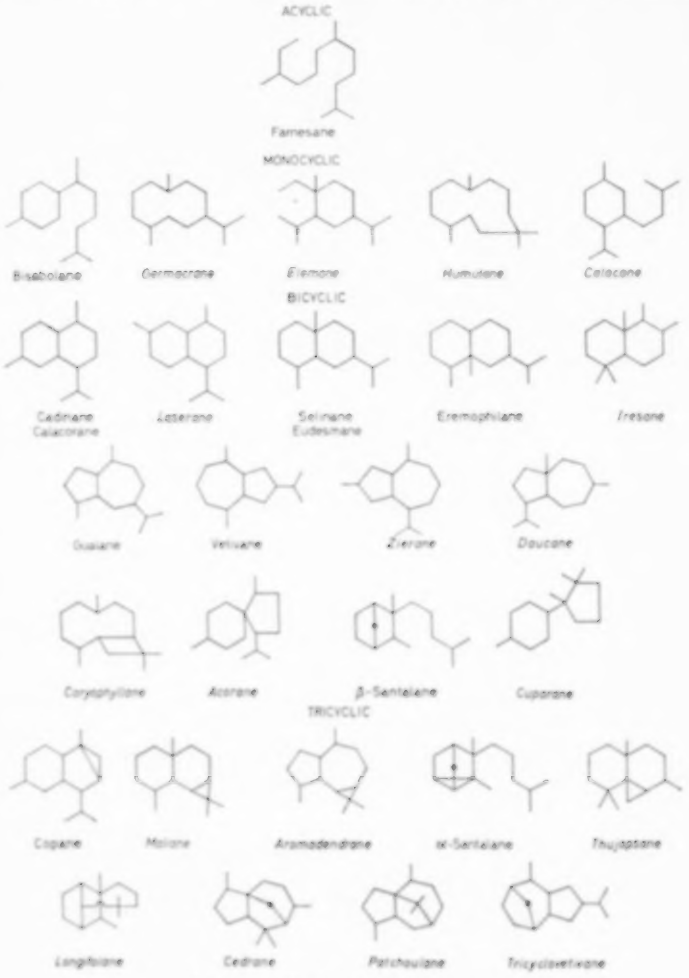
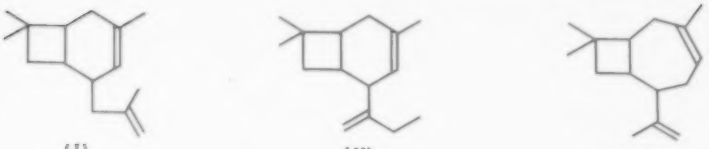


Figure 1. Types of sesquiterpenes

carbon skeletons known at present to occur in sesquiterpenes. The formulae with names printed *in italic* show structures which have been detected or firmly established within the last fifteen years, the others are older. The names of the various structural types are derived from the names of important hydrocarbons containing the appropriate carbon skeleton.

The size of the list in *Figure 1* shows clearly why it is impossible within the compass of a single lecture to summarize all our recent knowledge of

VOL. 2 1961



(I) Ruzicka (II) Treibs (III) Rydon

Figure 2

sesquiterpene chemistry; and, with your permission, I should like, therefore, to confine myself to a discussion of compounds known to contain medium-sized rings—I have in mind nine-, ten- and eleven-membered carbon rings. The discovery of such rings in common plant constituents was somewhat surprising, since until recently the existence of larger carbon rings had been established in Nature only in the macrocyclic fragrant ketones, and these, moreover, were products of animal metabolism. The difficulty of access by synthetic means to alicyclic compounds with medium-sized rings (which has only fairly recently been overcome by use of the acyloin condensation), as well as certain theoretical considerations concerned with their steric properties, only tended to confirm the view that compounds of this type were purely products of human thought and human labour.

The first proof of the occurrence of a medium-sized alicyclic ring in Nature was obtained in our Laboratory in 1949 in the course of our studies on caryophyllene[1].

Probably more work had been devoted to the elucidation of the structure of this compound than to any single other in sesquiterpene chemistry. It had been known for a long time that caryophyllene was a bicyclic hydro-

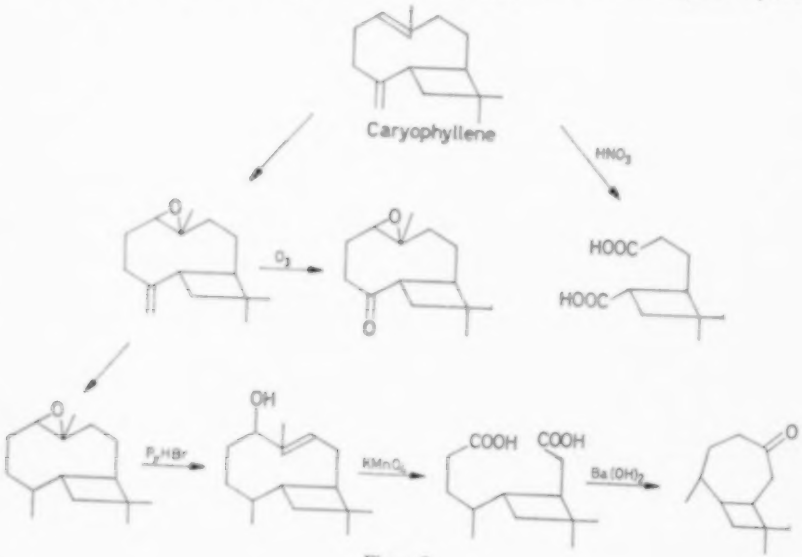


Figure 3

carbon containing two double bonds and a characteristic four-membered ring carrying *gem*-methyl groups. Originally, it had been our aim to decide between the three structures (I) proposed by Ruzicka, and (II), proposed by Treibs, and (III), proposed by Rydon[2] (*Figure 2*). As our starting-point, we chose the readily accessible oxido-ketone described by Treibs (*Figure 3*). Greatly to our surprise, the infra-red absorption spectrum of this compound showed a carbonyl frequency typical for a ketonic group situated on a medium-sized ring. To obtain further information about the size of the second ring, we carried out a degradation of this ring in dihydrocaryophyllene oxide by unambiguous steps involving the loss of two carbon atoms, one of them from the ring. Cyclization of the resulting dicarboxylic acid gave a ketone with a ring smaller by two members than the original

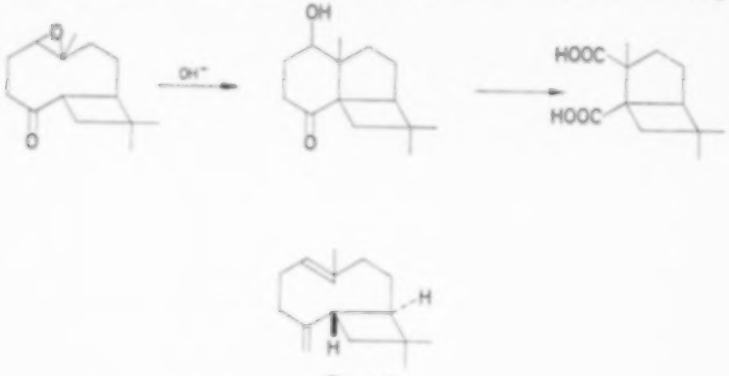


Figure 4

ring. This ketone still had an abnormally low carbonyl absorption in the infra-red (1705 cm^{-1}), corresponding to the presence of a seven-membered or, less probably, of a six-membered ring. Since tetrahydrocaryophyllene itself did not exhibit the infra-red absorption of an ethyl group, which is normally easily distinguished in saturated hydrocarbons and which would be expected to occur if the second ring were eight-membered, we considered the reaction sequence I have described to prove the presence of a nine-membered ring in caryophyllene. The C_{12}-ketone obtained in this degradation, and later prepared by partial synthesis[3], accordingly contained a seven-membered ring. I have discussed these reactions, by which the occurrence of a medium-sized ring in Nature was for the first time established, in some detail, since this work has often been reported as if we had based our conclusion, concerning the presence of a nine-membered ring, tentatively on the carbonyl frequency of Treibs' oxido-ketone alone.

Our degradative experiments permitted four formulations for caryophyllene. Two of these could be eliminated on consideration of the structure of homocaryophyllenic acid, an oxidation product of caryophyllene, as determined by Dawson and Ramage[4]. The carbon skeleton of caryophyllene was further confirmed by our partial synthesis of tetrahydrocaryophyllene[5]. The final decision between the remaining two formulae, differing in the position of the double bonds, and information about the stereochemistry of caryophyllene followed from the elegant work[6] of Barton, which

VOL. 2 1961

established the structure shown in *Figure 4*. The evidence was based first on the alkaline cyclization of Treibs' oxido-ketone to a tricyclic keto-alcohol and the further oxidation of this compound to the dicarboxylic acid. The annelation of the two rings is *trans*- and the double bond also has the *trans*-configuration in caryophyllene, but has the *cis*-configuration in the isomeric isocaryophyllene.

Recently, we have once more encountered the caryophyllene skeleton in two sesquiterpenic alcohols, the betulenols, isolated from the oil of birch buds (*Figure 5*)[7]. Treibs had already suggested some time ago that these compounds were related to caryophyllene. α-Betulenol is a bicyclic alcohol with two double bonds. Hydrogenation yields the saturated alcohol

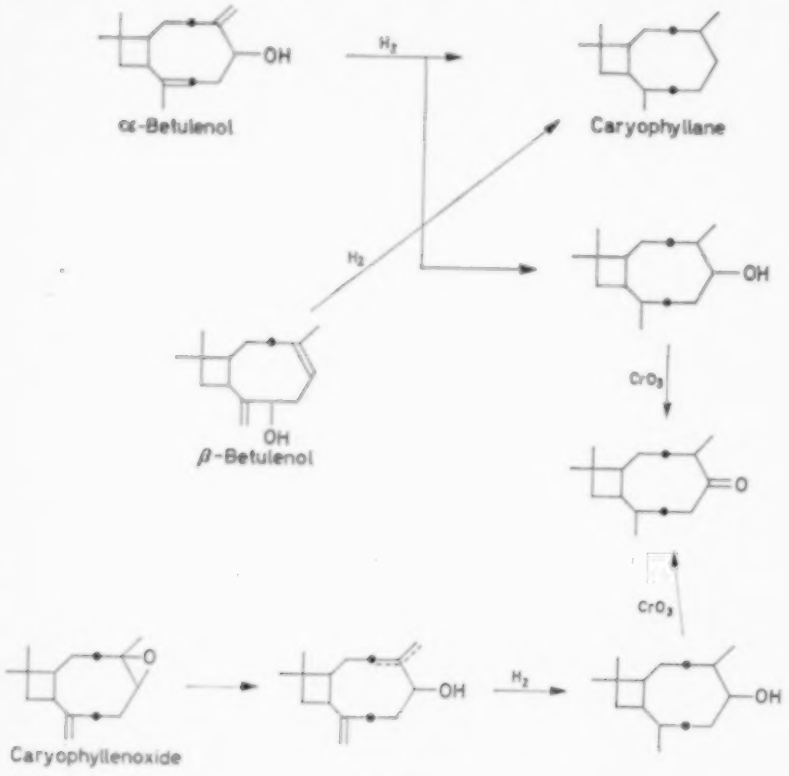


Figure 5

together with a hydrocarbon which has an infra-red absorption spectrum fully identical with that of tetrahydrocaryophyllene. This clearly demonstrates that α-betulenol belongs to the caryophyllane series. Oxidation of tetrahydrobetulenol with chromic acid gave a ketone which proved to be identical with a compound obtained from caryophyllene monoxide by an unambiguous reaction sequence; this establishes the position of the hydroxyl group. The crystalline β-betulenol is isomeric with α-betulenol, and the

chemical reactions and physical constants permitted us to allot the structure shown in *Figure 5* to this alcohol.

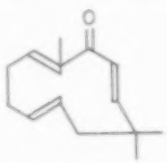
The hydrocarbon humulene was a further compound in which we were able to establish the presence of a medium-sized ring—in this case, an eleven-membered ring. Humulene is monocyclic and has three double bonds. Its structure was tentatively derived by us[8] and, shortly afterwards, by Clemo and his co-workers[9] from the fact that on oxidation it gives, in addition to α,α-dimethylsuccinic acid, only formaldehyde and acetic acid, and no higher monofunctional degradation products. A proper confirmation of the suggested skeleton was given by our total synthesis of hexahydrohumulene[10].

The position of the double bonds in humulene remained unsettled for some time. We first suggested the arrangement shown in *Figure 6* (*a*) on

(a) β – Humulene (b) α – Humulene

Figure 6

the basis of the ozonisation products and physical constants, especially the infra-red absorption at 890 cm^{-1} characteristic of vinylidene-type double bonds. Recently, Sutherland[11] and, independently, Dev[12] have come to the conclusion that pure humulene contains no exocyclic double bond and that the structure must be modified as shown in *Figure 6* (*b*). For this reason, we have recently returned to the study of humulene, after we had obtained a good supply of the hydrocarbon from the essential oil of the leaves of *Lindera strychnifolia*. Fractionation on a highly efficient column showed that with rising boiling-point there was a slight decrease in the content of exocyclic methylene groups. The highest content of exomethylene groups found was 0·36 per mole. When the distillation fractions were purified by Sutherland's method through the silver nitrate adduct, the resulting humulene contained only traces of exocyclic methylene; however, when the purified hydrocarbon was percolated through active alumina, material with a very high vinylidene content, about 83 mole per cent, was obtained. This material no longer forms a crystalline adduct with silver nitrate. Therefore, we conclude that the natural material contains two humulenes, which we call α- and β-humulene, in variable proportions. The α-isomer, without the exocyclic double bond, forms an adduct with



Zerumbone

Figure 7

VOL. 2 1961

silver nitrate, while the more stable β-humulene, which contains the exocyclic methylene group, forms no such adduct[13].

Some time ago, Bhattacharyya[14] and, independently, Dev[15] found that the sesquiterpene ketone zerumbone (*Figure 7*) also has the humulane skeleton; the chief evidence was again identification of the corresponding hydrocarbon with hexahydrohumulene by infra-red spectroscopy.

Sesquiterpenes containing a ten-membered carbon ring, especially oxygenated compounds, seem to be frequent products of plant metabolism, particularly in the Compositae. As I hope to show later, they are probably of some importance in the biogenesis of some other, bicyclic sesquiterpenes.

The first natural product for which a ten-membered ring structure was proposed was the lactone, pyrethrosine[16]. However, the first compound in which such a ring was definitely established was the ketone germacrone, the chief component of Bulgarian zdravets oil[17]. I think it will be instructive to recall the history of this interesting compound. It had been known for

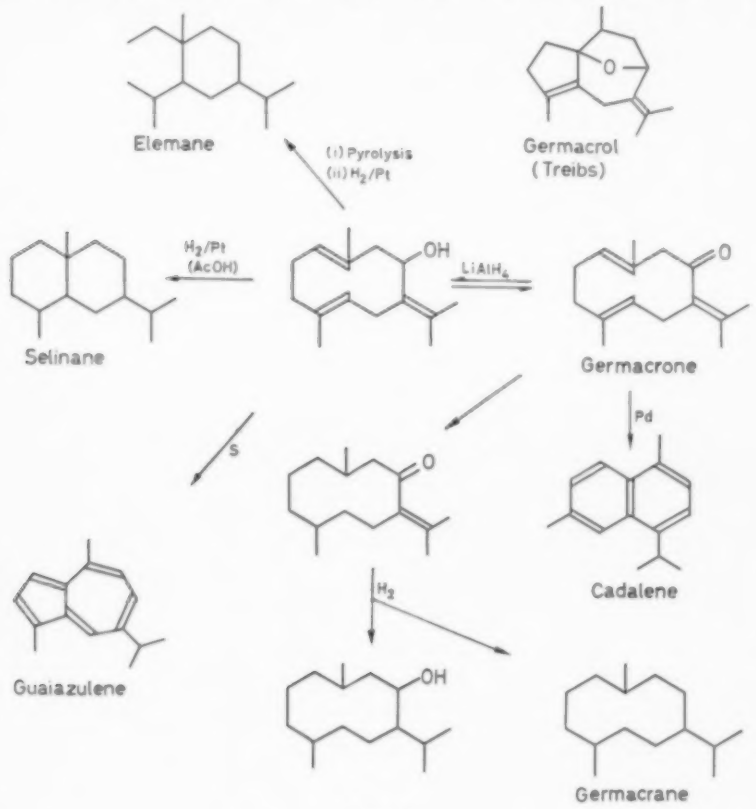


Figure 8

some time under the name germacrol, and studied in some detail by Treibs, who also proposed the first formula for it (*Figure 8*)[18]; as you see, he regarded it as a cyclic ether with a guaiane skeleton. When we set out to check this

structure, in co-operation with our Bulgarian colleagues, we found immediately, from the infra-red absorption spectrum, that we were dealing, not with an epoxide, but with a monocyclic unsaturated ketone. However, when we tried to hydrogenate or dehydrogenate germacrone (as we renamed it) we obtained surprising and contradictory results. After hydrogenation of germacrone (and germacrol) over platinum in acetic acid we isolated two hydrocarbons, both formed by hydrogenolysis. One was identified as monocyclic elemane by its infra-red absorption spectrum; the second was similarly identified as bicyclic selinane. Further, reduction of germacrone with aluminium isopropoxide or lithium aluminium hydride gave an alcohol, " germacrol ", which was converted back into crystalline germacrone by oxidation, and, on dehydration, gave a mixture of hydrocarbons which yielded considerable amounts of guaiazulene on dehydrogenation. Furthermore, it had already been shown previously that germacrone yields cadalene on dehydrogenation under fairly drastic conditions.

We see, then, that under various conditions, germacrone or its derivatives can be converted into derivatives of no less than four sesquiterpene types; of these, only the elemane-type corresponded to the presumed monocyclic nature of germacrone. Since it was difficult to visualize the formation of the other three types of skeletons from a compound based on the elemane skeleton, we concluded that germacrone was in fact derived from none of the four sesquiterpene types. We were able to confirm this as follows. Germacrone was first partially hydrogenated in ethanol (to prevent any

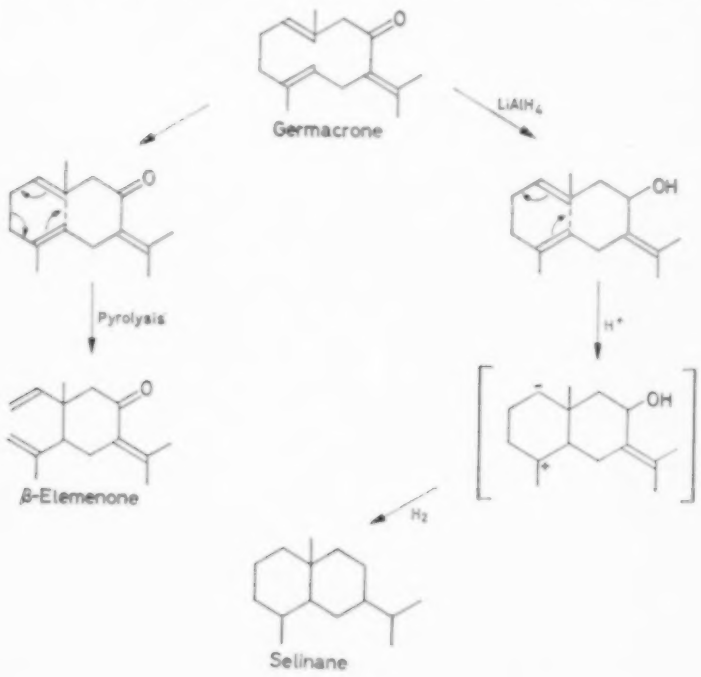


Figure 9

acid-catalysed cyclization reactions), and then further reduced in several steps. In this way we obtained a saturated alcohol—hexahydrogermacrol—and a hydrocarbon, whose infra-red absorption spectrum showed it to belong to a new sesquiterpene-type. We have called this the germacrane-type. All the reactions I have spoken of can be interpreted without difficulty if we assume that germacrone contains a ten-membered ring.

The location of the double bonds in germacrone proved somewhat difficult, especially because of its anomalous infra-red and ultra-violet absorption spectra. This difficulty even led to speculation on alternative formulae for germacrone. A structure based on the maaliane skeleton was suggested by Ohloff[19]. In fact, the explanation of the anomalous spectral properties of germacrone and some other ten-membered ring compounds such as costunolide lies elsewhere, as I hope to show later. Very recently, we have been able to fix the position of the double bonds in germacrone. Definite proof of the skeleton of germacrone was obtained by the total synthesis of germacrane[20].

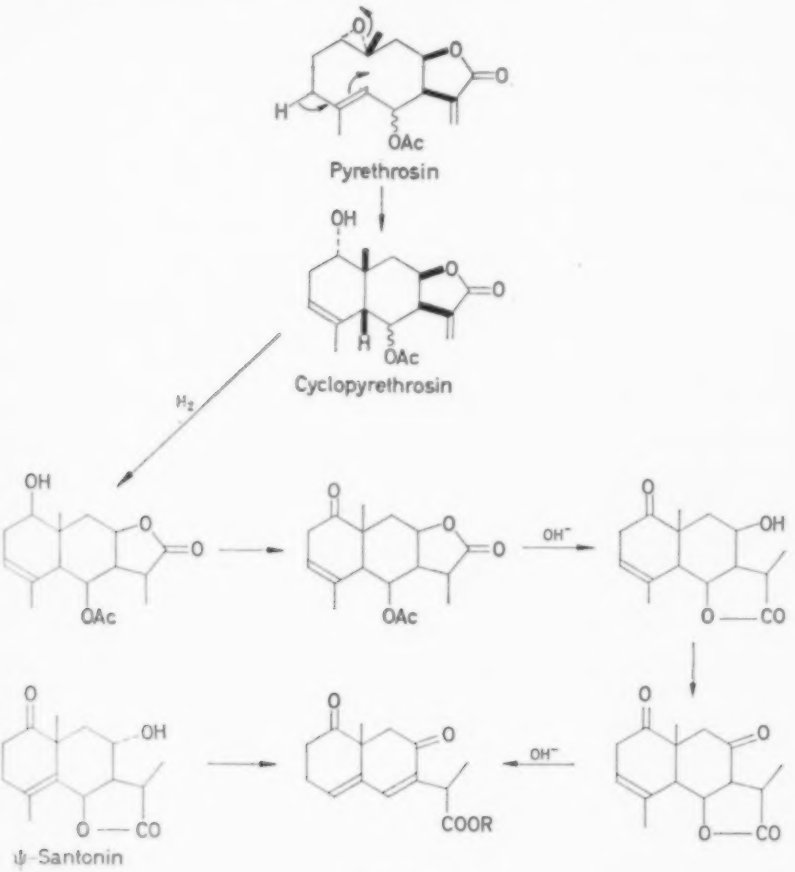


Figure 10

The reactions by which germacrone passes into compounds with other carbon skeletons are also readily interpreted on the basis of its structure (*Figure 9*). The transition into the elemane series is especially remarkable[21, 22]. Mere heating converts germacrone to the so-called β-elemenone. The position of the double bonds in germacrone is favourable for just this sort of reaction.

The conversions of germacrone into products of other sesquiterpene types, particularly of the selinane series, by hydrogenation and dehydrogenation can be interpreted as transannular cyclization reactions, and, as we shall see, such reactions have been encountered in a number of other cases.

Some years ago, the discovery of the guaianolides, a new group of sesquiterpene lactones somewhat similar to the santonin group but containing a guaiane skeleton, prompted us to undertake a detailed examination of the sesquiterpene lactones of the Compositae, and this search revealed a number of further compounds with ten-membered rings.

As I have already mentioned, Barton published his first paper on pyrethrosin[16], a lactone from *Chrysanthemum cinerariaefolium*, early in 1957, a few months before our publication on germacrone appeared (*Figure 10*). A key experiment in the structure determination proved to be an attempt at acetylation in acid solution which led to opening of the oxide ring, and formation of a bicyclic product named cyclopyrethrosin. The skeleton of this product was established by its conversion into an unsaturated diketo-acid which could be correlated with an oxidation product of pseudo-santonin. Recently, further studies on the reactions of cyclopyrethrosin and the physical properties of various derivatives have enabled Barton to establish the full structure of pyrethrosin and its cyclization product, and, in addition, to determine the configurations at most of the asymmetric centres[23].

During our investigations on the lactone arctiopicrin, the bitter principle of *Arctium minus*, we found that the molecular formula[24] which had been

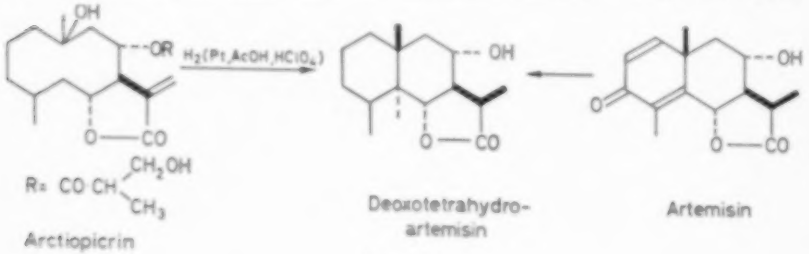


Figure 11

allotted to this compound was wrong, and that we were in fact dealing with the β-hydroxy-iso-butyric acid ester of a monocyclic sesquiterpenic hydroxylactone which we have called arctiolide[25, 26] (*Figure 11*). The most important evidence for its structure was derived by its relation to the santonin series. Hydrogenation of arctiopicrin in acid solution, followed by hydrolysis, gave a bicyclic compound which proved to be identical with deoxotetrahydroartemisin.

Some time ago, the Indian authors Rao, Kelkar, and Bhattacharyya[27] studied a sesquiterpene lactone, which they have called costunolide, from

VOL. 2 1961

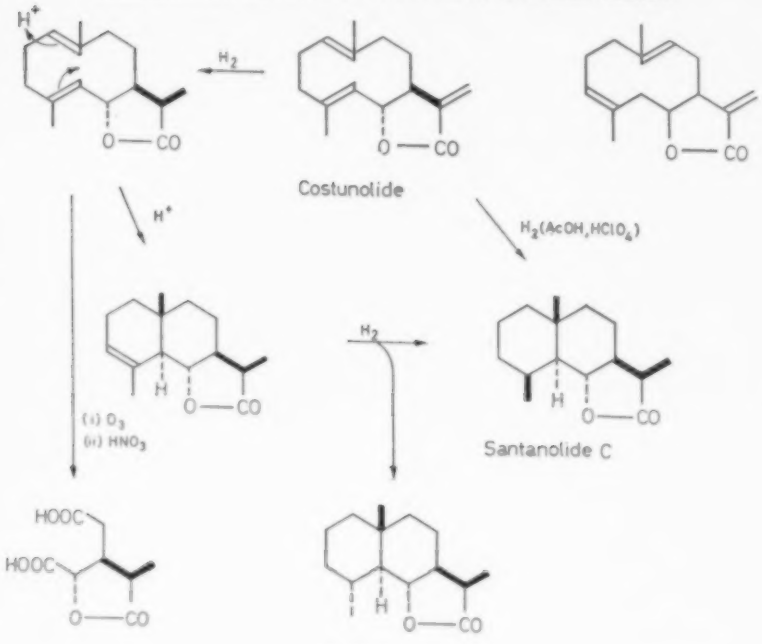


Figure 12

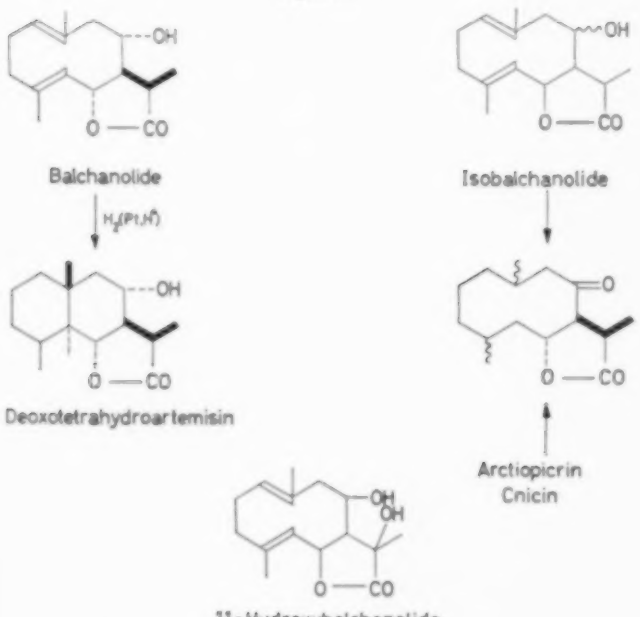


Figure 13

the Himalayan plant, *Saussurea lappa*. They showed that this lactone also contains a cyclodecane ring, and were able to propose two alternative formulae *a* and *b*. At about the same time, we were investigating the extractives of an Asian species of wormwood, *Artemisia balchanorum*; the main constituent proved to be a lactone which was evidently identical with costunolide. We were soon able to settle its structure and to show that it corresponded to formula *a* of the Indian authors, and to determine the absolute configuration of costunolide (*Figure 12*)[28]. Here again, stereospecific transannular cyclization reactions provided the key. Hydrogenation of costunolide in acid solution gave a product identified with santanolide C, one of the reduction products of santonin. Alternatively, dihydrocostunolide could be converted into an unsaturated bicyclic lactone; this proved identical with the 3-santenolide described by Cocker and McMurry[29], and, on hydrogenation, gave a mixture of santanolides A and C, compounds we had encountered earlier during our work on santonin. Since the absolute configuration of santonin is known, these reactions establish the configuration of costunolide. This was also confirmed later by Bhattacharyya and his co-workers[30].

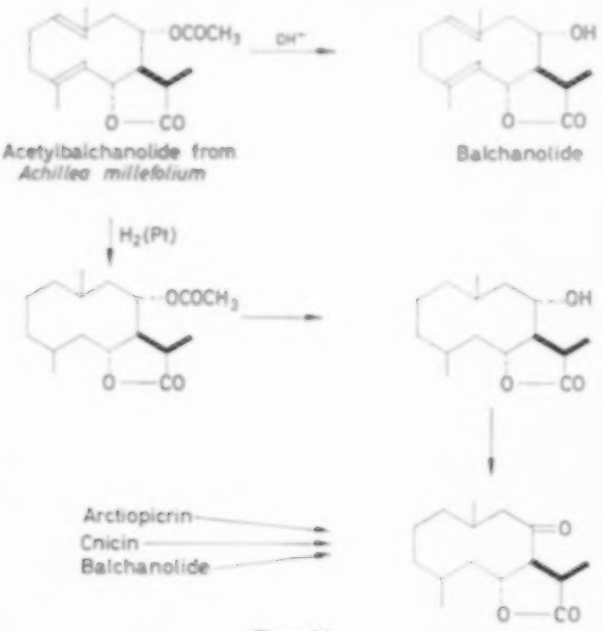


Figure 14

Costunolide is not the only lactone of *Artemisia balchanorum*. Paper chromatography of the extracts revealed at least four further compounds of this group, and three of these we have already obtained in crystalline form[31]. Each of them contains a cyclodecane ring. Two have identical compositions, and both contain two double bonds and one hydroxyl group; we have called them balchanolide and isobalchanolide (*Figure 13*). The

VOL. 2 1961

double bonds were located by oxidative degradation and, in the case of balchanolide, by transannular cyclization. Balchanolide can be cyclized under acid conditions in the usual way, or merely by heating it to about 170°. Hydrogenation of the product gave the same deoxotetrahydroartemisin as we had already encountered in our work on arctiopicrin. The constitution and configuration of isobalchanolide were confirmed by correlation with compounds derived from arctiopicrin. Oxidation of the hydroxyl group of tetrahydroisobalchanolide gave two isomeric ketolactones identical with products we had earlier obtained from arctiopicrin and cnicin. The detailed relation between balchanolide and isobalchanolide and their full stereochemistry remains to be settled.

The third crystalline lactone from *Artemisia balchanorum* is related to balchanolide—it is 11-hydroxybalchanolide.

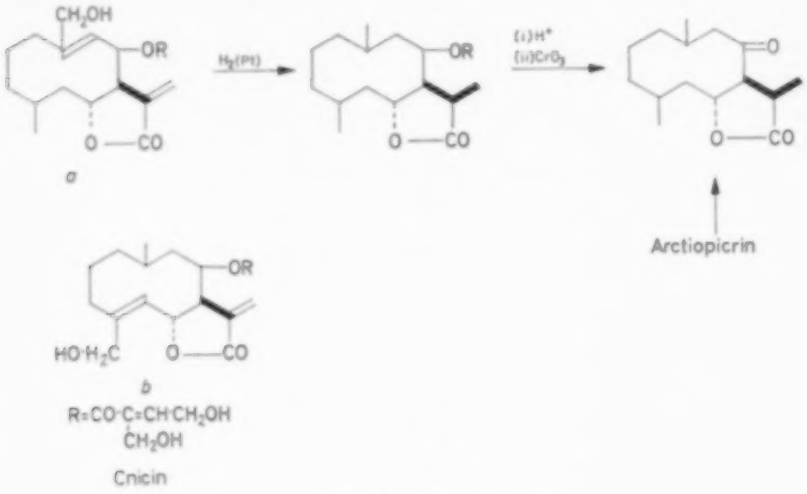


Figure 15

Recently we have found that a lactone isolated from the common milfoil (*Achillea millefolium*) is closely related to balchanolide[32]. It is the acetate of a doubly unsaturated hydroxy-lactone (*Figure 14*). Oxidation of the tetrahydro-derivative of the parent lactone obtained by hydrolysis led once more to the familar keto-lactone first prepared from arctiopicrin and cnicin. This suggested that our new lactone might be acetylbalchanolide; and, in fact, this was confirmed by a direct comparison of this compound with acetylated authentic balchanolide.

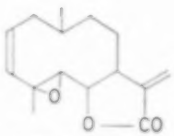
Another compound based on the germacrane skeleton is the bitter principle of *Cnicus benedictus*, a substance which has been known for more than a century, but again formulated erroneously until recently. We have shown that this compound, cnicin, is a monocyclic sesquiterpene hydroxylactone esterified with a rather uncommon carboxylic acid—1,4-dihydroxybut-2-ene-2-carboxylic acid. The parent lactone has two hydroxyl groups and two double bonds, one of them in conjugation with the lactone carbonyl group (*Figure 15*). Oxidation of the monohydroxylactone resulting from

hydrogenolysis and hydrolysis once more gave our well-known keto-lactone, and this establishes the position of the secondary hydroxyl group; the ready hydrogenolysis of the primary hydroxyl incidentally locates it in the allyl position to one of the double bonds, and, since some methylethylacetic acid is also split off hydrogenolytically, the esterified hydroxyl group also appears to be next to a double bond. These facts make it likely that cnicin has the structure *a*, or, less probably, *b*[33, 34].

Yet another compound of the germacrane group was found in partheno-lide, a lactone isolated in our laboratories from *Chrysanthemum parthenium*[35]. Parthenolide contains two double bonds, one of them conjugated with the carbonyl group, and a third oxygen atom present as an ether bridge (*Figure 16*).

I should now like to come back to some of the special features of these ten-membered ring compounds. The great ease with which unsaturated derivatives of germacrane undergo stereospecific transannular cyclization, most generally to compounds with a selinane skeleton—that is, in the case of the lactones, into relatives of santonin—suggests a biogenetic significance of such reactions. It appears likely that the cyclodecane-type lactones are the primary products in Nature, and that lactones of the santonin and guaianolide series are formed from them by secondary processes analogous to the stereospecific transannular reactions. A further pointer in the same direction is the frequent occurrence of lactones of the germacrane series in the Compositae in which santonin derivatives commonly occur. Within a brief space of time, nine closely-related lactones of the germacrane-type have been isolated from plants of this Family, and fully characterized. None-theless, actual proof of the occurrence of such cyclization reactions in Nature is still lacking.

VOL. 2 1961



Parthenolide

Figure 16

Some of the unusual reactions observed with medium-sized ring com-pounds, especially the ready transannular cyclizations of the cyclodecane derivatives, are without doubt the result of specific steric conditions in these compounds. The same cause lies at the root of the spectroscopic anomalies which have been noted with some compounds of this series, and which have a precedent in the anomalous spectrum of cyclodecenone recorded by Leonard[36]. I should like to discuss this point in a little more detail.

Germacrone (*Figure 8*) shows three maxima in the ultra-violet absorption spectrum at 213, 240, and 315 mμ. The second and third may be allotted to the unsaturated ketone grouping; but the short-wave maximum is difficult to interpret on the basis of the classical relations between structural and spectral properties. The same maximum is also found in the alcohol, germacrol, and in a number of the natural unsaturated lactones such as

costunolide, balchanolide, isobalchanolide and acetylbalchanolide. Therefore, this feature is not bound up with the carbonyl group of germacrone, but is evidently related to the character of the two endocyclic double bonds in the cyclodecane ring.

The anomalies in the ultra-violet absorption spectra of the cyclodecadiene derivatives I have discussed suggested to us the possibility of " non-classical " interactions of the endocyclic double bonds, which might well be expected to affect the spectra. Therefore, we asked Dr Koutecký, of the Institute of Physical Chemistry of our Academy, to verify this possibility by the appropriate quantum-mechanical calculations. From a consideration of models, Dr Koutecký and his co-workers, Dr Zahradník and Dr Paldus, concluded that in all three geometrical isomers of cyclodeca-1,5-diene—that is, the *cis,cis-*, *cis,trans-*, and *trans,trans*-isomers—conformations could be set up in which the double bonds were roughly parallel. *Figure 17* shows

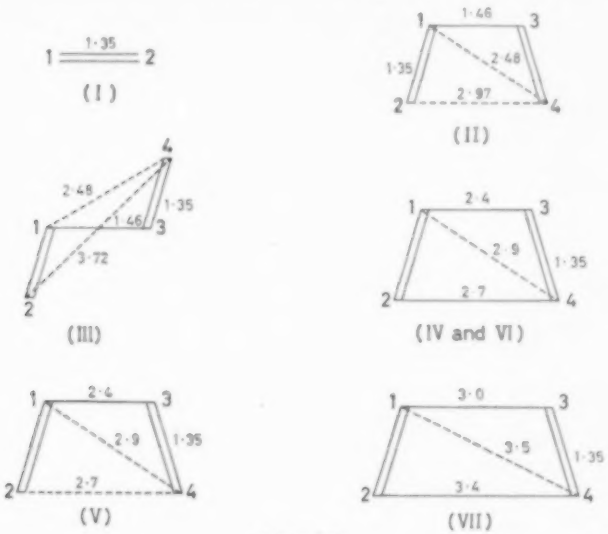


Figure 17.
(Broken lines: distances between non-bonded atoms ($\beta ij = 0$))

the four spatial arrangements of the relevant four carbon atoms of the cyclodecadiene molecule for which calculations were made, together with ethylene and *cis-* and *trans*-butadiene. The energies of transition from the highest occupied to the lowest vacant energy level were calculated by a self-consistent molecular orbital method; the results for ethylene and *cis-* and *trans*-butadiene were used to check the suitability of the chosen parameters. As *Table 1* shows that the delocalization energies for three of the models are negligible, and only for model (V), with a decreased β_{24} integral, is its value appreciable. *Table 1* also shows the results of calculations of the absorption frequencies in Clar's classification. From our point of view, the most important is the highest wavelength singlet *p*-band. The calculated values for ethylene and the butadienes are in good agreement with experimental values; all the cyclodecadiene models considered show a relatively

Table I. Delocalization energy and frequency of singlet *p*-bands for models (I)–(VII)

Model	*Delocalization energy* (kcal/mol)	*p**
(I)	—	7·38 (170)
(II)	13·2	5·18 (239)
(III)	12·2	5·39 (230)
(IV)	0·6	4·47 (277)
(V)	5·5	5·68 (218)
(VI)	0·2	5·65 (219)
(VII)	0·2	6·30 (197)

* Frequencies in eV; for singlet *p*-bands also in mμ (in brackets).

marked interaction, and in particular, models (V) and (VI) give values for the singlet *p*-band very close to the observed absorption maxima of germacrone, costunolide and dihydrocostunolide. Therefore, the results of these calculations show that transannular interaction of the double bonds in our cyclodecadiene derivatives is not only theoretically possible, but in fact very probable.

Now let us consider the infra-red absorption spectrum of germacrone. This shows the expected absorption associated with a conjugated carbonyl and trisubstituted double bonds; however, the spectra of ketones containing a tetrasubstituted double bond in conjugation with the carbonyl bond generally show a very strong maximum at about 1620 cm^{-1}, and this is absent from the absorption spectrum of germacrone. Originally, this fact led us, and later Ohloff, to consider the possibility that germacrone might contain a reactive cyclopropane ring; but it appears now that the true cause of this anomaly is very probably once more the specific geometry of the ten-membered ring in germacrone. An inspection of models shows that some conformations in particular force the carbon–oxygen double bond out of the plane of the tetrasubstituted ethylenic double bond, and this presumably leads to the observed change in the spectral properties.

I have dealt with these spectroscopic anomalies in some detail because they show how the investigation of novel types of compounds can be complicated by lack of experience even when well-tried methods are used.

On this note I should like to close my talk, in which I have tried briefly to recall the history of research on medium-sized ring terpenes, and to present some recent results from this field.

I should like to mention the colleagues who were especially active in this work. They were Drs V. Herout, L. Dolejš, M. Suchý, M. Streibl, V. Jarolím and M. Souček.

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VOL.
2
1961

SOME ASPECTS OF TERPENOID AND STEROID CHEMISTRY

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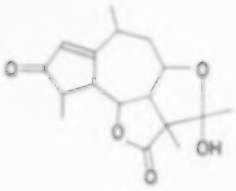
The lactonic bitter principles comprise an important group of natural substances. If we exclude from consideration the coumarins, compounds which do not present great difficulties in structural elucidation, then there remains a large family of bitter principles whose biogenesis appears to be of the terpenoid (mevalonic acid) type. Compounds of this latter kind have presented challenging problems for generations, but it is only in the last decade that their constitutions have received serious attention. Because of the limited time available for this lecture, only work from our own group can be discussed. This does not, of course, mean that others have not also been making important contributions to the field.

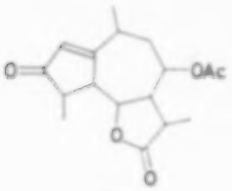
We may commence by listing some of the interesting constitutions that our group has studied during the last few years. First comes tenulin (I)[1], chiefly remarkable for the ease with which it rearranges under very mildly alkaline conditions (boiling London tap water!) into isotenulin (II), which has a true acetate grouping. Secondly, we may mention lactucin (III)[2], a compound of alleged medicinal value, which has an interesting cross-conjugated dienone system. Thirdly, comes geigerin (IV)[3], a compound to which we shall make further reference later. Fourthly, let us consider pyrethrosin (V)[4], of especial interest as it was the first sesquiterpenoid in which a ten-membered ring was shown to be present. This feature was recognized as being of biogenetic significance, a view which has been abundantly confirmed by later work[5]. These compounds contain sesquiterpenoid skeletons based directly upon a cyclized farnesol chain without rearrangement of the carbon skeleton[6]. The diterpenoid derivative, columbin (VI), the main bitter principle of Colombo root, is different in that the two methyl groups have, according to biogenetic hypothesis, been moved from their original positions in a skeleton as in (VII)[7].

These examples will serve to show the wide variety of functional groups that one finds in the lactonic bitter principles. The problems of structural elucidation are, in fact, as difficult as one wishes to make them. Perhaps we can illustrate this, as well as the interesting types of reaction that can be discovered incidentally to the investigations, by considering our recent work on the citrus bitter principles. Limonin is the characteristic bitter principle of citrus species occurring in all parts of the plant. The literature on this compound has been detailed in a recent paper[8], and we shall cite here only those references especially pertinent to our own work.

Our investigations on the constitution of limonin were initiated in Glasgow in 1956, and have been continued to the present time. From the outset, we



(I)



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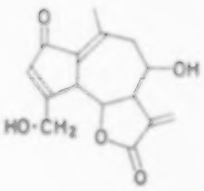

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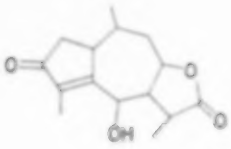

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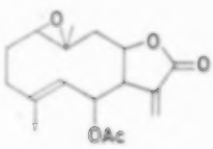

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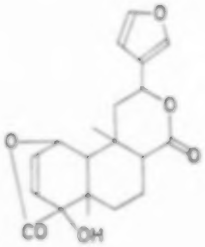

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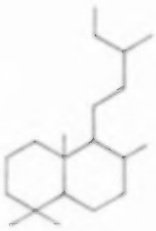
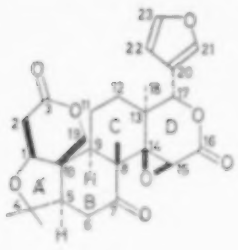


(VII)

collaborated with Professor Robertson in an X-ray investigation which eventually (see below) made an important contribution to the problem.

Chemical work on the constitution of limonin has also been in progress in Zürich in the laboratories of Professor Jeger and Dr Arigoni, and at Urbana, Illinois, under the direction of Professor Corey. During the last three years, there has been an exchange of information and free discussion of the problem, and the conclusions reached on the chemical side (summarized in a recent joint communication[9]) represent a collaborative effort. We shall make reference to the X-ray work at Glasgow[4] and to other chemical investigations where this is relevant to our presentation.

The constitution and stereochemistry of limonin, $C_{26}H_{30}O_8$, can be represented[9–11] as in (VIII). From the biogenetic point of view, the compound is a tetracyclic triterpenoid of the euphol (IX) type[12] from which four carbon atoms at the end of the side chain have been removed and carbon atoms C–20 to C–23 then converted into a furan ring. Ring A of the triterpenoid skeleton has been oxidatively cleaved between C–3 and C–4, and the C–3-carboxyl thus formed oxidatively cyclized on to C–19. The constitution of limonin also requires an oxidative cleavage of the Baeyer-Villiger type upon a 16-ketone in the skeleton of (IX) to give the



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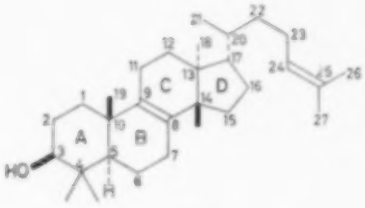

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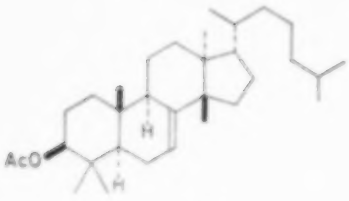

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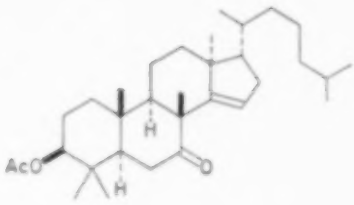


(XI)

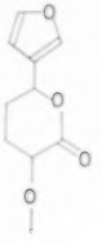
ring D lactone. Finally, one methyl group must be migrated from C–14 to C–8. It is of interest that chromic acid oxidation of dihydrobutyrospermol acetate (X) furnishes the compound (XI)[13] which has a 7-ketone group, an ethylenic linkage between C–14 and C–15 and a β-methyl group moved from C–14 to C–8. It is attractive to suppose that an equivalent mechanism operates in the plant in the biogenesis of limonin. The numbering and lettering systems in limonin (VIII) follow directly from these biogenetic considerations, and are the same as in other tetracyclic triterpenoids[14].

The absolute configuration of limonin, expected from the biogenetic arguments developed above, has been confirmed by the rotatory dispersion curve[15] method[9], the measurements being kindly made by Professor Klyne of the Postgraduate Medical School, London.

Work published either before, or during, our own investigations had shown[8,9] that limonin contains two δ-lactone rings, which can be opened reversibly with alkali, a β-substituted furan residue, a ketonic oxygen present in a six-membered (or larger) ring, and two ethereal oxygen cycles. Hydrogenation of limonin gives tetrahydrolimonin, $C_{26}H_{34}O_8$, and hexahydrolimoninic acid, $C_{26}H_{36}O_8$. The furan ring is saturated in both compounds, and the acid is formed by hydrogenolysis of one of the lactone rings. There is good evidence[8,9] that this lactone cleavage is caused by having the alkyl oxygen of the lactone in the allylic relationship to the furan ring. An exactly comparable situation is found in columbin[7]. Hexahydrolimoninic acid is abnormally strong[16], a fact which is conveniently explained by attaching one of the ethereal oxygen atoms in the α-position. The part formula (XII) is thus established[8].

The ketone group of limonin can be reduced stereospecifically by the Ponndorff–Meerwein procedure[17] to give the axial alcohol limonol ((XIII): R = OH; R′ = H). On the other hand, reduction with borohydride or with sodium amalgam gives the equatorial epilimonol ((XIII): R = H; R′ = OH). We have converted epilimonol into its chloroacetate and thence into the iodoacetate ((XIII): R = H; R′ = O·CO·CH_2I). It is the latter compound which was used in the X-ray work of Robertson and his colleagues[10].

Treatment of limonin with hydriodic acid gives first deoxylimonin, $C_{26}H_{30}O_7$ (XIV)[16], and then citrolin, $C_{26}H_{28}O_6$ [16, 18]. Further reference to these compounds is made below.



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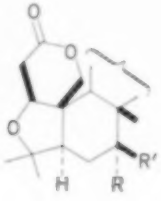

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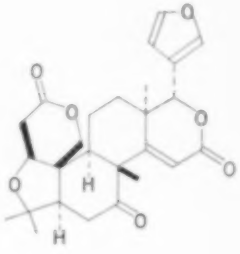

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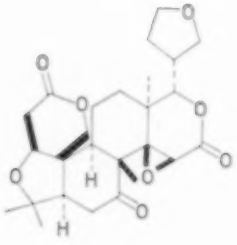

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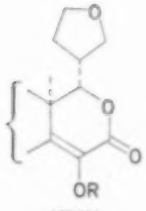


(XVI)

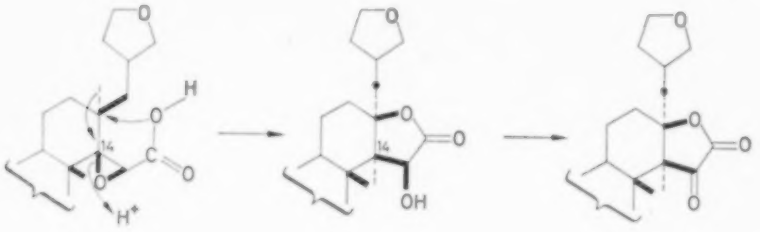
The molecular formula of limonin, when coupled with knowledge of the functional groups, requires that the molecule be bicarbocylic. Since drastic degradation[19] of limonin yields 1,2,5-trimethylnaphthalene, one can assume tentatively that the two carbocycles are both six-membered.

We now develop our own arguments in support of the constitution (VIII). The formation of the α,β-unsaturated lactone deoxylimonin from the action of hydriodic acid on limonin suggests the presence of a 1,2-epoxide[20]. Conjugation of this epoxide with the ring D lactone is shown by the fact that treatment of tetrahydrolimonin (XV) with hydrochloric–acetic acid mixture under controlled conditions gave iso-tetrahydrolimonin, an enolized α-keto-lactone ((XVI): R = H), characterized as its acetate ((XVI): R = Ac). The presence of the enolic system, established by a ferric reaction

and by spectroscopic data, was confirmed by ozonolysis followed by mild hydrolysis, a procedure which yielded oxalic acid.

Treatment of tetrahydrolimonin with hydriodic acid under controlled conditions gave deoxytetrahydrolimonin (as (XIV)), also prepared by selective hydrogenation of deoxylimonin (XIV). Deoxytetrahydrolimonin was, as expected, stable to acid under the conditions specified above. This and other experiments indicated that the second ethereal oxygen was probably not present as a 1,2- or 1,3-epoxide.

The action of hydrochloric acid–acetic acid on hexahydrolimoninic acid (XVII) gave a neutral isomer containing (from the infra-red absorption spectrum) a γ-lactone ring. This is formulated as (XVIII) and, in agreement, oxidation with pyridine–chromium trioxide afforded an α-keto-

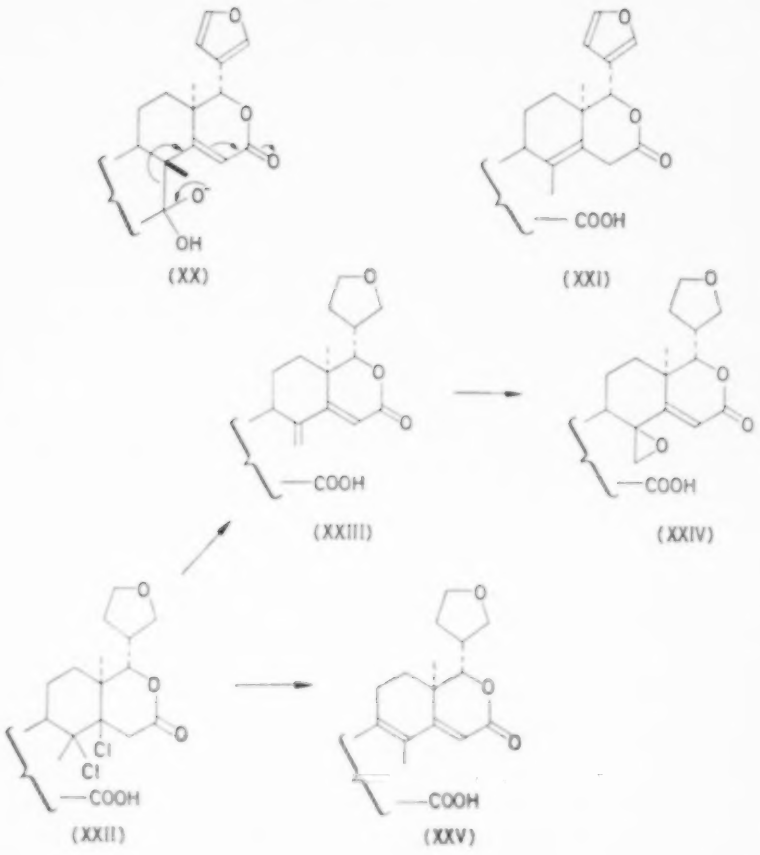


(XVII) (XVIII) (XIX)

lactone (XIX) which could *not* be made to enolize. One must conclude from this that the original isomerization of (XVII) has placed a new carbon–carbon bond at C–14 in accordance with the formula (XVIII). Our own work does not prove that the migrating group is methyl. This is, however, shown conclusively by work carried out at Zürich and Urbana[9].

The relationship between the ketone group of limonin and the lactone ring D was disclosed by the following experiments (and also other work[9]). Treatment of deoxylimonin (XIV) under lactone titration conditions gave a non-conjugated carboxylic acid, $C_{26}H_{32}O_8$, which still retained the two lactone residues but no longer responded to spectroscopic or chemical tests for the ketone group. Deoxylimonin oxime is stable under the same conditions of alkalinity so that it must be attack by hydroxyl ion upon the ketone group which initiates the reaction. All these facts are consistent with a reaction course indicated by the arrows in (XX) to give (XXI) as the structure of the acid, now conveniently designated as deoxylimonic acid. Similarly, deoxytetrahydrolimonin (as (XIV)) gave deoxytetrahydrolimonic acid (as (XXI)).

The further reactions of deoxytetrahydrolimonic acid have confirmed the structure assigned. It reacted with one mole of chlorine to give an adduct ((XXII) or equivalent) which was too unstable to be isolated. Heating *in vacuo* afforded a mixture of two crystalline diene-acids, both characterized as their methyl esters. The major product had a broad absorption band at 255 mμ and a low ϵ value (7800) in agreement with a *cisoid*-diene-structure (XXIII). It gave formaldehyde on ozonolysis and had three vinyl-type

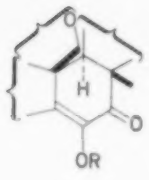


protons in its nuclear magnetic resonance spectrum, two ($\tau = 4{\cdot}60$ and $4{\cdot}38$) indicative of an exocyclic methylene group, or equivalent structure, and one ($\tau = 3{\cdot}97$) consistent with the presence of a vinyl hydrogen α- to a lactone grouping (as in ring D). The acid (XXIII) was further characterized as the epoxide (XXIV) which showed a normal α,β-unsaturated lactone spectrum comparable to that of deoxylimonin. The minor product from heating (XXII) was a *transoid*-diene-lactone (XXV) as shown by its ultra-violet absorption spectrum [λ_{max} 230 and 284 mμ ($\epsilon = 6{,}300$ and 16,400 respectively)]. These two diene-lactones not only confirm the relationship of the C–7 ketone of limonin to the ring D lactone, but also show the presence of a methyl group at C–8 and of a hydrogen atom at C–9.

The environment of the C–7 ketone group of limonin was defined in a simple manner. Limonin in dry tert.-butanol containing potassium tert.-butoxide was rapidly autoxidized to give the diosphenol ((XXVI): R = H) characterized as its acetate ((XXVI): R = Ac). Analogous diosphenols

VOL. 2 1961

((XXVII) and (XXVIII) respectively) were obtained from deoxylimonin (XIV) and tetrahydrolimonin (XV). These compounds show that limonin contains the system $-\overset{\beta}{C}H-\overset{\alpha}{C}H_2-CO-$. The position of the ultra-violet absorption spectrum maximum near 280 mμ further indicated that there was very probably only one β-H with respect to the ketone of limonin in the partial formula given above.



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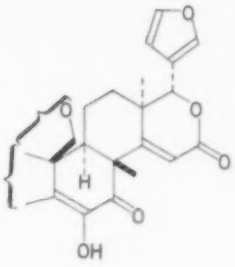

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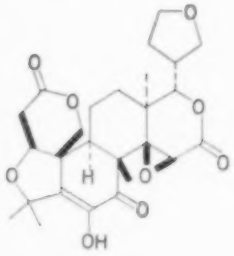

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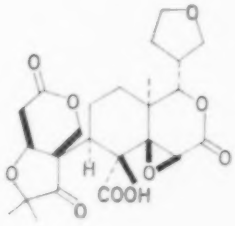


(XXIX)

These diosphenol formulations were further confirmed by the ozonolysis of the derivative (XXVIII) from tetrahydrolimonin. This gave in good yield a nor-acid (XXIX), characterized as its methyl ester. Treatment of this acid with aqueous alkali gave formaldehyde. The presence of the grouping $-CO-O-CH_2-\overset{|}{\underset{|}{C}}-C=O$ in the nor-acid (XXIX) is thus established. In its infra-red absorption spectrum, the methyl ester of (XXVIII) showed a carbonyl band at 1760 cm^{-1}. This cannot be due to either lactones A or D, for the trisodium salt (two lactones opened and the carboxyl group neutralized) still showed a carbonyl band near 1750 cm^{-1}. It must be ascribed to the new ketone function produced in the ozonolysis. This enhanced frequency is consistent with a cyclopentanone with an α-ethereal substituent.

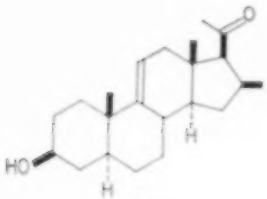
The reaction of carbanions derived from ketones (or equivalent functional groups) with oxygen would appear to be of more significance in degradational and synthetic chemistry than is normally appreciated. Two recent communications are illustrative.

Some steroidal ketones with a progesterone-type side chain react smoothly

with oxygen in potassium tert.-butoxide solution to furnish 17-α-hydroperoxides[21]. For example, the ketone (XXX) gives the hydroperoxide (XXXI) which can be reduced in high yield by zinc dust and acetic acid to the corresponding alcohol (XXXII). The insertion of the 17-α-hydroxyl into ketone (XXX), required for the building up of the adrenocortical-type side chain, is not so readily accomplished by more conventional methods.

The carotenoid canthaxanthin (XXXIII) reacts with oxygen under the above specified conditions to give astacene (XXXIV)[22]. This is a reaction which cannot be accomplished by other methods.

Limonilic acid, $C_{26}H_{30}O_9$ [16], was first obtained[18] by oxidation of limonin in alkaline solution with potassium permanganate, but it is more readily prepared in essentially quantitative yield by treatment of an alkaline solution of limonin with hypoiodite[16]. Limonilic acid is to be formulated as (XXXV)[9]. Its method of formation represents a new procedure for



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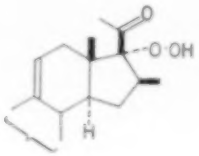

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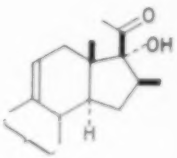

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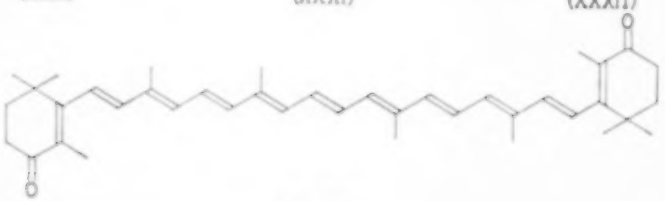

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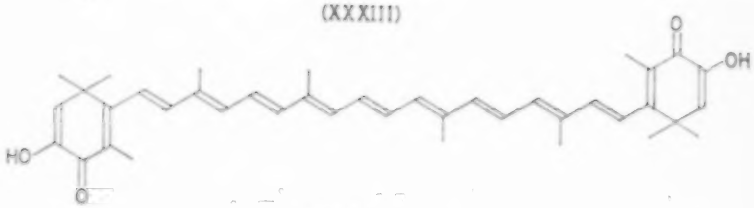

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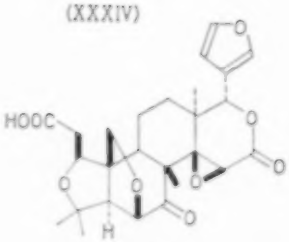
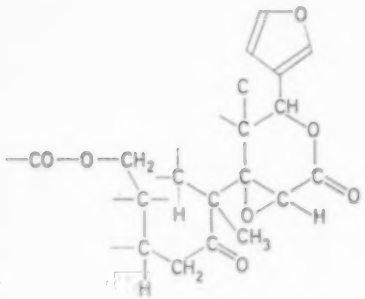


(XXXV)

VOL. 2 1961

making an ethereal linkage, facilitated, no doubt, by a specially favourable conformational situation.

The work of our group outlined above, coupled with earlier published work on limonin, makes it possible to write without ambiguity the part structure (XXXVI). If we accept a triterpenoid type of biogenesis[9], and have regard to the formation of acetone in high yield on fusion with potassium hydroxide[16] and to the formation of naphthalenic products[8, 19] on dehydrogenation, then one can write (XXXVII) as a plausible formula for limonin (see Arigoni *et al.*[9]). This was the position in September, 1959, when Professor Robertson was able to state from the X-ray evidence (see Arigoni *et al.*[9]) that limonin was either (VIII) or (XXXVIII). The latter formula is, of course, incompatible with much chemical evidence, and therefore formula (VIII) stands. In addition, the X-ray work provides the complete stereochemistry of the molecule.



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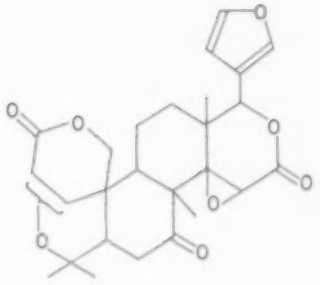
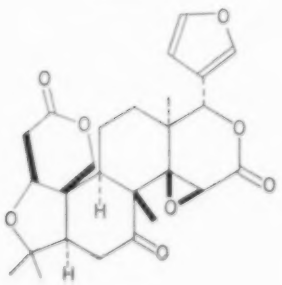
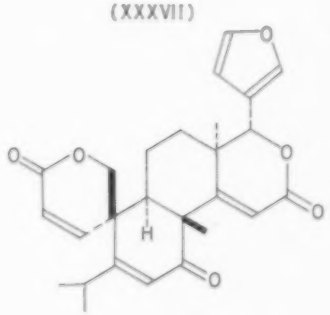


(XXXVII)



(XXXVIII)



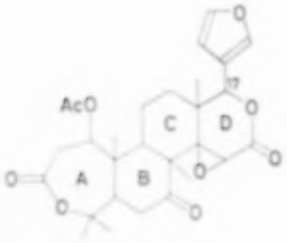
(XXXIX)

The formulae (VIII) and (XIV) for limonin and deoxylimonin respectively permit the formulation of citrolin as (XXXIX). The earlier work of Emerson[16] had established that citrolin contained an α,β-unsaturated ketone function as well as an α,β-unsaturated lactone and a furan ring. A study of the hydrogenation of citrolin[16] appeared to show that these were the only unsaturated groupings present. We noted, however, that the ultraviolet and infra-red absorption spectra of citrolin were in better accord with the presence of *two* α,β-unsaturated lactone groups. This was confirmed by the selective hydrogenation of citrolin (under conditions which

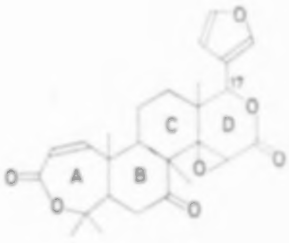
do not attack the unsaturation of ring D) to give a dihydrocitrolin ((XXXIX) ring A saturated). In this compound, the presence of a saturated δ-lactone ring could be seen directly in the infra-red absorption spectrum, and indirectly by differential ultra-violet spectroscopy with respect to deoxylimonin (XIV). The nuclear magnetic resonance spectrum of citrolin confirmed the presence of 4 C—Me groups.

The two minor bitter principles of citrus species are nomilin, $C_{28}H_{34}O_9$, and obacunone, $C_{26}H_{30}C_7$ [23]. They have recently been investigated further by Dean and Geissman[24]. Both compounds contain two lactone rings (one of which can be opened reversibly, the other irreversibly), a furan ring, a somewhat unreactive ketone group and an ethereal ring. Nomilin is a β-acetoxy-lactone which, on treatment with a suitable hot tertiary amine, is converted into the α,β-unsaturated lactone obacunone with elimination of acetic acid. Upon consideration of these and other published facts discussed in more detail below, and having regard to a probable biogenetic relationship to limonin, we proposed[11] the formulae (XL) and (XLI) for nomilin and obacunone respectively. The work that we summarize below, whilst not yet providing a complete proof of the correctness of these structures, is, nevertheless, in full accord with them, and confirms many of the functional group relationships. In addition, we have resolved certain anomalies in the earlier work[24] which were in apparent disagreement with our proposed formulae.

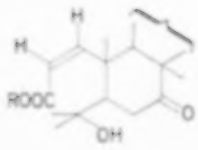
Both nomilin and obacunone, on mild treatment[23, 24] with alkali, afford obacunoic acid, $C_{26}H_{32}O_8$ ((XLII): R = H), in which the A ring lactone has been opened irreversibly as expected of a seven-membered ring.



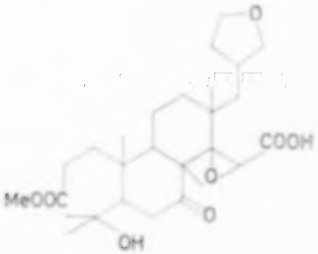
(XL)



(XLI)



(XLII)



(XLIII)

VOL. 2 1961

Obacunoic acid has two active hydrogens, in keeping with the presence of a normal alcoholic hydroxyl group, a feature about which there was some confusion earlier[24]. Methyl obacunoate[24] ((XLII): R = Me) likewise showed an OH band of a normal type in the infra-red absorption spectrum. The nuclear magnetic resonance spectrum of ((XLII): R = Me) confirmed the presence of four normal C—Me groups (τ = 8·88, 8·97, 9·008 and 9·043), one C—Me (τ = 8·618) of the type at C-13 in limonin (that is, close to the furan ring), and of a *cis*-β-substituted acrylic ester (A–B quartet at τ = 4·24 and 4·49 (α-H) and at τ = 3·798 and 4·08 (β-H); J_{AB} = 13·4 c/sec; see Jackman[25]). In addition, two α-hydrogens (τ = 2·506) and one β-hydrogen (τ = 3·658) attached to a furan ring[26] could be seen easily. One proton with a τ value of 4·63 indicated >CH—O— at C-17, a feature seen in the nuclear magnetic resonance spectra of limonin and its derivatives.

On hydrogenation in acetic acid over palladized charcoal, obacunoic acid consumed 3·74 mols of hydrogen. Methyl obacunoate behaved similarly (3·86 mols uptake), and gave a crystalline methyl ester acid (XLIII) through hydrogenolysis of the D-ring lactone just as in limonin (see above). The consumption of hydrogen in our hands is one mol less than that observed earlier[24]. We conclude, therefore, that obacunone and nomilin are bicarbocyclic like limonin, not monocarbocyclic as proposed[24] earlier on the basis of the hydrogenation evidence.

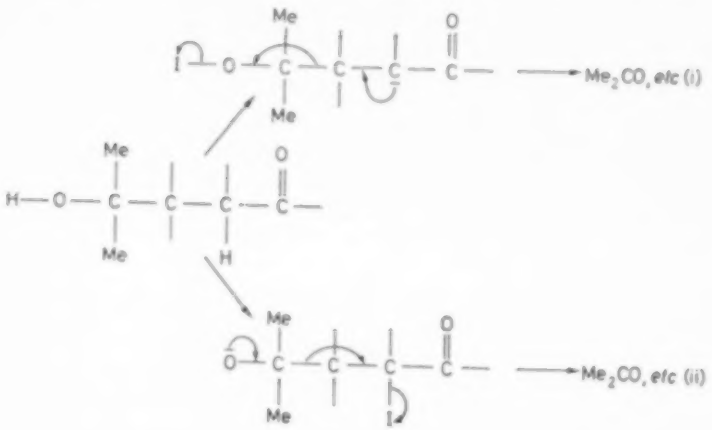
Obacunoic acid behaved like limonin on reduction with chromous chloride[9], and afforded a crystalline deoxyobacunoic acid. This contained an α,β-unsaturated lactone ring regarded as δ- because of its frequency in the infra-red absorption spectrum. A similar conclusion as to the size of the reversibly opened (D-ring) lactone can be reached from the infra-red absorption spectra of all obacunoic acid derivatives. Deoxyobacunoic acid behaved like deoxylimonin (see above) in that mild treatment with base gave a product which, on spectroscopic evidence, now lacked the α,β-unsaturated lactone ring. It could not be crystallized, but was clearly an analogue of deoxylimonic acid (XXI).

Another analogy between limonin and obacunoic acid could be seen in the following transformation. Treatment of the methyl ester acid (XLIII) with dioxan–hydrochloric acid under the conditions needed to transform hexahydrolimoninic acid (XVII) into its rearranged isomer (XVIII) gave an acidic product which, from its infra-red absorption spectrum, was also a γ-lactone (frequency at 1785 cm^{-1}). In addition, this substance showed α,β-unsaturated ketone absorption in its ultra-violet absorption spectrum, but with a carbonyl frequency in the infra-red absorption spectrum which was abnormally low (1630 cm^{-1}). The same anomalously low carbonyl frequency is found in (XVIII) (1686 cm^{-1}), and must be due to hydrogen bonding with the C-15-hydroxyl. In (XVIII), the γ-lactone frequency is also rather high at 1789 cm^{-1}. The reaction product is, therefore, formulated as an analogue of (XVIII), although again it could not be crystallized.

On mild treatment with sodium methoxide, methyl obacunoate was converted into a compound conveniently designated iso-obacunoic acid (XLIV). This substance lacked the α,β-unsaturated acid function of obacunoic acid, and also (see below) the hydroxyl group. The facts are conveniently explain by formula (XLIV) and, indeed, the formation of

such an iso-acid is in full accord with the proposed[9] (see also above) biogenesis of limonin.

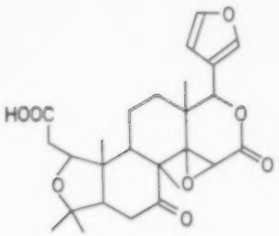
Dean and Geissman[24] made the interesting observation that obacunone gives a positive iodoform test. Under standard conditions[27], the following yields of iodoform (in parentheses) were obtained: acetophenone (30 per cent), acetonedicarboxylic ester (16, 21 per cent), obacunoic acid (15 per cent), limonin (0 per cent), iso-obacunoic acid (0 per cent), cinnamic acid (0 per cent), crotonic acid (0 per cent). These results show that it is the hydroxyisopropyl grouping of obacunoic acid which is responsible for the test. There are two obvious mechanisms which would explain this:



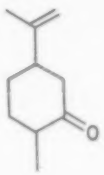
Route (i) would appear more probable, but we do not have any decisive experiment to distinguish between the two. We have shown, however, that suitable model compounds react in the same way. Thus, whilst dihydrocarvone (XLV)[28] gave no iodoform, its hydrate (XLVI)[29] gave 4 per cent. Similarly, carvone furnished no iodoform, but its hydrate ((XLVII): X = O)[30] gave 6 per cent. From the latter reaction, the expected 4,6-diiodo-*o*-cresol ((XLVIII): R = H), characterized as its 3,5-dinitrobenzoate, could be isolated. α-Terpineol ((XLVII): X = H_2) gave no iodoform, but dihydroisophotosantonic lactone ((XLIX): X = H)[31], where an analogous mechanism as indicated by the arrows in ((XLIX): X = I) can operate, gave 4 per cent. These iodoform experiments, taken as a whole, suggest that obacunoic acid has an hydroxyisopropyl group separated by two carbon atoms from the ketone group as already written into formula ((XLII): R = H).

The environment of the ketone group of obacunoic acid was further defined by autoxidation experiments of the kind already described (see above) for limonin and its derivatives. Alkaline autoxidation of obacunoic acid gave a diosphenol, characterized as its acetate, in the manner expected. However, the ϵ values for these compounds were significantly lower than for compounds of the limonin series, and both the diosphenol and its acetate analysed for one H_2O less than expected. In addition, both compounds

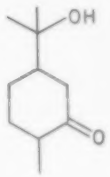
VOL. 2 1961



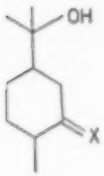
(XLIV)



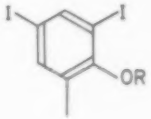
(XLV)



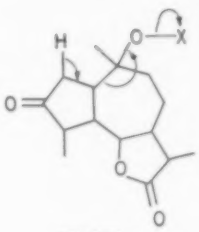
(XLVI)



(XLVII)



(XLVIII)



(XLIX)

were neutral, not acidic. Formulae which explain these facts are (L), (LI) and (LIII); according to this scheme, a normal diosphenol acid (L) is first formed, but it then rearranges, if only fleetingly, to (LI), collapse of which (see arrows in (LI)) gives the diosphenol ((LIII): R = H).

Autoxidation of iso-obacunoic acid gave an acidic diosphenol with the normal spectroscopic and chemical properties expected of (LII). However, it could not be crystallized.

If all the facts on obacunoic acid are summarized, and the interpretations made in the deduction[9] of the limonin structure are repeated, then, assuming also that the lactone ring A of obacunone is 7-membered, the part expression (LIV) for obacunone can be derived fairly rigidly.

The stereochemistry of obacunone is not defined by the above experiments. However, the change in $[M]_D$ between limonin and epilimonol is almost exactly the same as that between obacunone and α-obacunol, the borohydride reduction product of obacunone[24], indicating an analogous stereochemical environment. The change in $[M]_D$ from obacunoic acid to deoxyobacunoic acid is not, however, in good agreement with the corresponding change in the limonin series. We assumed that obacunone was related, stereochemically as well as constitutionally, to limonin and was thus (LV). An attempt to interrelate limonin and obacunone was, therefore, initiated along the following lines.

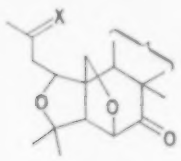
Limonilic acid (XXXV) was transformed into the corresponding methyl ketone ((LVI): X = O) by a standard series of reactions[32], and the latter was then converted into the dithioketal derivative ((LVI): $X = (S—CH_2)_2$). Preliminary experiments showed that limonilic acid could be reduced back efficiently to limonin by the use of lithium amalgam, and that a typical dithioketal was not reduced by this reagent under the experimental conditions

employed. Treatment of ((LVI): X = $(S—CH_2)_2$) in this way, and oxidation of the product with pyridine–chromium trioxide, then furnished the keto-aldehyde (LVII). Conversion of the aldehyde group to methyl should afford a derivative of iso-obacunoic acid. So far, however, it has not been possible to reduce the aldehyde of (LVII) without damaging other functional groups in the molecule.

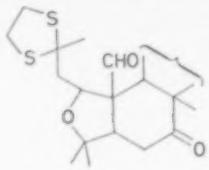
A preliminary communication by Kubota, Kamikawa, Tokoroyama and Matsuura[33] has been published in which independent evidence is presented for the part structure (LVIII) for obacunone. All the observations of the Japanese authors are in agreement with our proposed formula (XLI) for this bitter principle.

From consideration of lactonic bitter principles derived from the common triterpenoid–steroid type of biogenesis, we return again to sesquiterpenoid chemistry for an account of some recent work on geigerin carried out in collaboration with Dr Pinhey[34]. Bromination of geigerin (IV) acetate with *N*-bromosuccinimide gave a derivative whose constitution and stereochemistry were shown by X-ray crystallography[35] to be as in (LIX). At

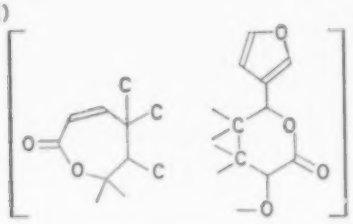
VOL. 2 1961



(LVI)

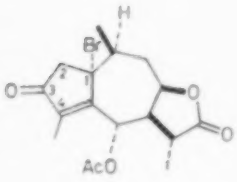


(LVII)

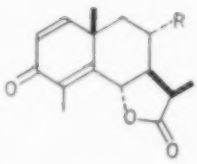


(LVIII)

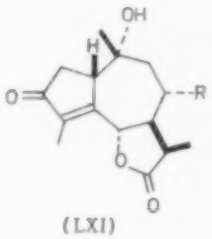
the same time, a direct correlation between artemisin ((LX): R = OH) and geigerin has confirmed certain aspects of the X-ray investigations[35], and has proven the absolute stereochemistry of geigerin since that of artemisin was already known[36].



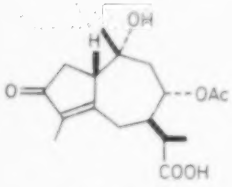
(LIX)



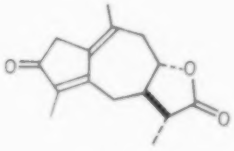
(LX)



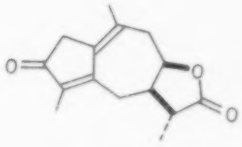
(LXI)



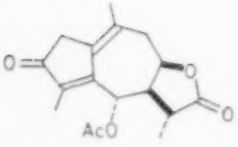
(LXII)



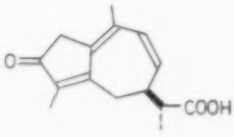
(LXIII)



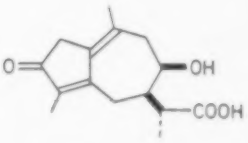
(LXIV)



(LXV)

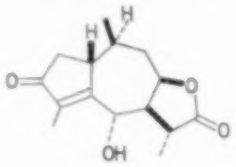


(LXVI)



(LXVII)

Some years ago, we showed[31] that santonin ((LX): R = H) was rearranged by irradiation with ultra-violet light in aqueous acetic acid to give the lactone ((LXI): R = H). This is a general reaction[37, 38] with obvious applications in the synthesis of naturally occurring perhydroazulene derivatives. Irradiation of artemisin acetate gave a photo-product[38] ((LXI): R = OAc) which, on reduction with chromous chloride, gave the acid (LXII). Treatment of the latter with perchloric acid in acetic acid under controlled conditions furnished the dienone (LXIII). On dissolution in 1 per cent ethanolic potassium hydroxide at room temperature and immediate acidification, the dienone (LXIII) gave an isomeric dienone (LXIV) identical with anhydrogeigerin[3, 34]. The latter can be obtained from geigerin in various ways and, in particular, from the bromo-derivative (LIX) by refluxing with dimethylformamide to give (LXV), followed by reduction of this with chromous chloride. The inversion of configuration on treating (LXIII) with alkali can be easily understood as vinylogous β-elimination to the trienone (LXVI), followed by immediate β-directed (from the β-oriented side-chain) readdition of carboxylate anion with (ultimately) normal hydrolysis of the lactone group to give the hydroxy-acid (LXVII). The mildness of the alkaline conditions precludes inversion at position 11 (in the side-chain) which, in any case, is the same[36] in both artemisin and geigerin[35]. The absolute stereochemistry of geigerin is thus established at all centres except C–1 (see (LIX)). A β-configuration at this centre has been assigned on the basis of rotatory dispersion studies[39], so that geigerin can be represented in full detail as in (LXVIII):



(LXVIII)

It is a pleasure to acknowledge that the work described in the present lecture has been done by my able colleagues Drs J. T. Pinhey, S. K. Pradhan and S. Sternhell and by Mr J. T. Templeton.

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VOL
2
1961

STRUCTURAL PATTERNS OF POLYACETYLENIC COMPOUNDS ISOLATED FROM THE PLANT FAMILY COMPOSITAE

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INTRODUCTION

The Compositae constitute one of the largest plant Families. No modern botanical treatment of the whole family exists, but a simplified survey of the Family, taken from the 70 years' old review by Hoffmann[1], is given in *Table 1*. A few ordinary garden flowers or well-known weed genera are mentioned as examples, and, for simplification, some trivial tribus-designations are also given. Most botanists agree on a division of the Family into

Table 1. Simplified survey of the Family of the Compositae

Botanical Tribus	*Common Genus*	*Trivial Tribus Designation*	*Approximate Number of Genera in Tribus*
I Vernonieae	*Vernonia*	Ironweeds	41
II Eupatorieae	*Eupatorium*	Thoroughworts	42
III Astereae	*Aster* (*Solidago*) (*Bellis*)	Aster (Goldenrods) (Daisy)	99
IV Inuleae	*Gnaphalium* *Antennaria* (*Inula*)	Everlastings	152
V Heliantheae	*Helianthus* (*Dahlia*) (*Cosmos*) (*Bidens*) (*Coreopsis*)	Sunflowers	144
VI Heleniеae	*Helenium* (*Tagetes*)	Sneezeweeds (African Marigolds)	55
VII Anthemideae	*Chrysanthemum* (*Artemisia*) (*Matricaria*)	Chrysanthemum	49
VIII Senecioneae	*Senecio*	Groundsel	51
IX Calenduleae	*Calendula*	Marigolds	8
X Arctotideae	*Arctotis*		11
XI Cynareae	*Centaurea* (*Cirsium*) (*Arctium*)	Thistles	34
XII Mutisieae	*Gerbera*	Gerbera	57
XIII Cichorieae	*Taraxacum* (*Hieracium*)	Dandelions	63
			Total: 806

13 tribes. It will be seen that, in 1889, the 13 tribes of the Compositae comprised more than 800 genera. Although monotypic genera also exist in the Compositae, most of the genera contain numerous species: some, for example *Senecio*, have more than 1000, and many contain more than 200 well-defined species. The definition of species in some cases, *e.g. Taraxacum* (dandelions) and *Hieracium* (hawkweeds), is among the most dubious known to botanists. Clearly no exact statement can be given of the number of species; depending on personal choice of definition, the number will be somewhere between 15,000 and 100,000. Perhaps some 250–300 good species have been investigated for the occurrence of acetylenic compounds. I hope this fact will show you the caution we shall have to exercise in taxonomic application of our really very preliminary results.

The botanist has long since used a phytochemical characteristic, the ability to produce a milksap, to divide Tribus XIII Cichorieae, to which both the dandelions and hawkweeds belong, from the rest of the Family. As far as present investigations go, this tribe seems to be devoid of the enzymatic systems leading to polyacetylenes, and so we can leave them out of consideration.

TYPES OF ACETYLENIC COMPOUNDS

VOL. 2 1961

Carboxylic acids

Derivatives of acids, *viz.* methyl esters and isobutylamides, constitute the simplest types of acetylenic compounds found in the Compositae.

In a pocketbook for chemists and druggists edited in 1826[2] by Bretz and Elieson, it is stated that the essential oil from the root of European mugwort, *Artemisia vulgaris*, deposits yellow crystals in the cold. For more than 100 years no chemist took interest in these crystals, and so the first observation of naturally occurring polyacetylenic compound in the solid state remained unheeded. In 1950, these slightly yellow crystals were shown by my collaborators to be the 2-methyldec-2-*cis*-ene-4,6,8-triynoate[3], which was given the trivial name *cis*-dehydro-matricaria ester. Its constitution, together with those of the six other members of this series so far isolated from higher plants, is given in *Table 2*.

My naming of these esters may be heavily criticized. The 2-*cis*, 8-*cis*-matricaria ester has been found most abundantly and most frequently, and so this compound was named after *Matricaria inodora* L. (= *M. maritima* L.), the common scentless mayweed.

I prefer to retain a trivial name for the 8,9-dihydro- esters. The *cis*-isomer was isolated in 1935 by Viljams, Smirnov and Goljmov[4] from the essential oil of *Lachnophyllum gossypinum* Bge. These Russian scientists established the constitution unambiguously with the aid of classical degradation methods. The *cis*-lachnophyllum ester was the first naturally occurring diacetylenic compound whose structure was elucidated. It is also most unusual in being a polyacetylenic compound which has been used in industry. Local Russian perfume industries transformed the odourless *cis*-lachnophyllum ester into soap perfumes by treatment with weak alkali. Curiously enough, these perfumes are still of unknown constitution.

Table 2. Acetylenic-C_{10} methyl esters from Compositae

Constitution of ester	*Trivial name of ester*	*Genera in which ester has been found*
$H_3C \cdot CH_2 \cdot CH_2 \cdot C{:}C \cdot C{:}C \cdot CH{:}CH \cdot COOCH_3$	*cis*-lachnophyllum ester[4]	*Lachnophyllum*, *Erigeron*
	trans-lachnophyllum ester[5]	*Bellis*
$H_3C \cdot CH{:}CH \cdot C{:}C \cdot C{:}C \cdot CH{:}CH \cdot COOCH_3$	2-*cis*,8-*cis*-matricaria ester[6]	*Matricaria* (*Tripleurospermum*), *Erigeron*
	2-*trans*,8-*cis*-matricaria ester[7]	*Matricaria* (*Tripleurospermum*), *Amellus*
$H_3C \cdot CH{:}CH \cdot C{:}C \cdot C{:}C \cdot CH_2 \cdot CH_2 \cdot COOCH_3$	8-*cis*-α,β-dihydro-matricaria ester[7]	*Matricaria* (*Tripleurospermum*), *Amellus*
$H_3C \cdot C{:}C \cdot C{:}C \cdot C{:}C \cdot CH{:}CH \cdot COOCH_3$	*cis*-dehydro-matricaria ester[8]	*Artemisia*, *Achillea*
	trans-dehydro-matricaria ester[6]	*Matricaria* (*Tripleurospermum*), *Achillea*

The compilation in *Table 2* demonstrates that the configuration at the ethylenic bonds in these esters is frequently *cis*. The stability of the *cis*-configuration in these esters is remarkable; they remain unchanged when treated with iodine in the presence of light according to the standard techniques of isomerizing *cis*-carotenoids. Only the classical techniques for producing the light-induced equilibration of *trans*-stilbene with *cis*-stilbene cause a partial transformation, the conversion in this instance being from 2-*cis* to 2-*trans*.

In some of the Compositae, only *cis*-isomers occur; but others have mixtures of *cis*- with minor amounts of *trans*-isomers, and sometimes *trans*-dehydro-matricaria ester may even be found stereochemically pure. All these facts indicate that the *cis*- and *trans*-isomers are genuine components of these plants. It should be mentioned, however, that some of the crude chromatographic fractions show a rather strong allene peak at 1960 cm^{-1}, and, at least in the daisy, *Bellis perennis*, there occur components which give free *trans*-lachnophyllum acid on saponification[5]. These components have never been found in amounts sufficient for final purification, but, according to spectrographic studies, both the conjugated system of lachnophyllum acid and the *trans*-double-bond are produced during the saponification. I have mentioned this preliminary work on the acetylenes of the daisy to emphasize my belief that my collaborators have not as yet encountered all the variations which the Compositae produce on the simple theme of unsaturated C_{10}-acids.

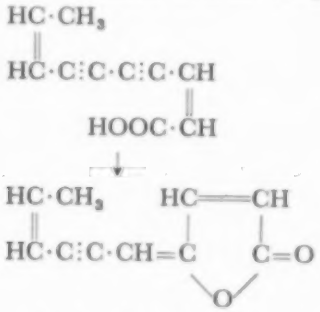
The methyl esters in *Table 2*, however, are easily recognized compounds; some of them crystallize extremely readily, and most of them possess very characteristic ultra-violet light absorption properties. In spite of this, these esters have so far only been isolated from 2 of the 13 tribes of the Compositae: *viz.*, III Astereae and VII Anthemideae. Although caution is necessary at this early stage of our investigation, I am inclined to

believe that this fact is connected with the taxonomic division of the Family. In the Aster tribe III, the few acetylenes found have all been C_{10}-compounds; but in the Chrysanthemum tribe VII, many different types of acetylenes have been found, with 10, 12, 13, 14, 15 and 17 carbon atoms per molecule.

Although investigations for acetylenic compounds in other plant Families have been few and accidental, it is remarkable that, so far, these compounds have been encountered only in the Basidiomycete group of the higher fungi, instanced by the finding of Jones and his collaborators that 2-*trans*,8-*trans*-matricaria ester is present in *Polyporus anthracophilus*[9], and *trans*-dehydromatricaria acid in *Pleurotus ulmarius* [10].

In the culture medium of these fungi, the acetylenic acids occur to some extent as methyl esters, but mostly as free acids. That free acids are synthesized also in the Compositae became clear when Christensen, in collaboration with the Jones school, elucidated the constitution of the so-called " Composit-cumulene I "[11] which was isolated in my laboratory in 1950 as a crude liquid from the leaves of scentless mayweed (see *Figure 1*, curve B). At that time I supposed it to be both a pure compound and a cumulene, though in fact it was neither.

In 1953 Miss Holme was able to isolate the main constituent of "Composit-cumulene I " as a few mg of a crystalline compound, m.p. 35·5°, from a *Chrysothamnus* species (see *Figure 1*, curve A). In connection with efforts to synthesize the naturally occurring 2-*cis*-isomers of the lachnophyllum, matricaria and dehydromatricaria esters, Bell, Jones and Whiting observed a rapid formation of lactones from the *cis*-acids in sodium bicarbonate solution. Christensen[13] demonstrated that the 2-*cis*,8-*cis*-matricaria acid lactonizes very rapidly in all polar solvents, and that the transformation in water is completed in a few minutes at room temperature:



Hence, it is obvious that the free 2-*cis*-4-ynoic acids will never be found in a biological medium. The corresponding lactone from *cis*-lachnophyllum acid is a liquid. Christensen has demonstrated its presence in some of those Compositae which are rich in the corresponding ester, *e.g. Boltonia asteroides* (L.) L'Her and *Erigeron acris* **rigidus* Fr.[14].

Clearly the free acetylenic acids are also produced by the higher plants, but lactonization prevents them accumulating and, as is clear from *Figure 1*, causes spectral changes which hamper recognition of their acetylenic nature.

VOL. 2 1961

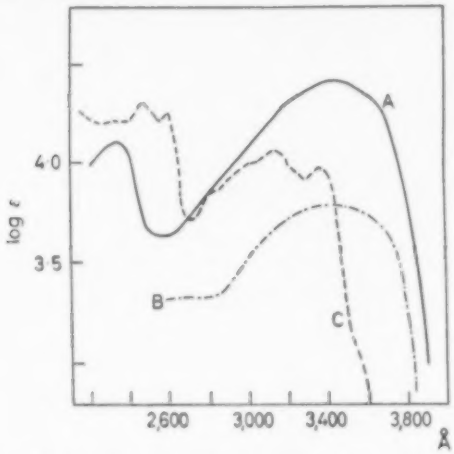


Figure 1. Ultra-violet light absorption spectra in hexane of: A. 4-hydroxy-deca-2,4,8-trien-6-ynoic acid, γ-lactone; B. "Composit-cumulene I", according to Sørensen and Stavholt[11]; C. *cis,cis*-matricaria ester

The only other derivatives of acetylenic acids isolated from Compositae are isobutylamides. As a result of the work of Crombie, anacyclin and dehydro-anacyclin (two of the insecticidal compounds of the *Anacyclus pyrethrum* D.C. extract) have been shown to contain acetylenic bonds.

$$H_3C\cdot CH_2\cdot CH_2\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH_2\cdot CH_2\cdot CH{:}CH\cdot CH{:}CH\cdot CO\cdot NH\cdot CH_2\cdot CH(CH_3)_2$$

Anacyclin

$$H_3C\cdot CH{:}CH\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH_2\cdot CH_2\cdot CH{:}CH\cdot CH{:}CH\cdot CO\cdot NH\cdot CH_2\cdot CH(CH_3)_2$$

Dehydro-anacyclin

The most potent isobutylamides known at the moment are those which have purely ethylenic unsaturation, but, on examination of side-fractions during systematic research on the isolation of potent insecticidal principles, co-existing acetylenic compounds may be discovered.

I might add that such compounds as anacyclin are also easily overlooked for two other reasons. Firstly, their acetylenic chromophore does not give rise to any readily recognizable strong band in the ultra-violet light absorption spectrum; and, secondly, the extraction of these amides requires rather special solvents. According to biological work, many members of the Compositae have a pyrethrum-effect similar to the isobutylamides, and so there is a distinct possibility that the acetylenic isobutylamide group is much more widespread than we appreciate today.

From a purely chemical point of view, the most interesting fact is the chain length and the degree of unsaturation. By both tokens anacyclin and dehydro-anacyclin are intermediate between the ordinary unsaturated fatty acids and the C_{10}-acids of the Compositae.

Alcohols

None of the other classes of acetylenic compounds are as simple as the carboxylic acids. Whereas the Basidiomycetes studied by the Jones school

very often produce a methyl ester as well as the free carboxylic acid and the corresponding primary alcohol, this has never been observed in higher plants.

As will be seen from *Table 3*, which gives a compilation of the primary alcohols isolated in my laboratory from Compositae, the alcohol corresponding to the matricaria ester has been found in two stereoisomeric forms, only one of them (the 2-*trans*,8-*cis*) corresponding to the configuration of the methyl esters.

Table 3. Esters of acetylenic alcohols isolated from the Compositae

Constitution of acetylenic alcohol	*Stereochemistry*	*Genus*
$H_3C{\cdot}CH{:}CH{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	2-*trans*,8-*trans* 2-*trans*,8-*cis*	*Aster* *Xanthisma*
$H_3C{\cdot}CH{:}CH{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	4-*cis*	*Brachycome*
$H_3C{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	5-*cis*	*Matricaria*
$H_2C{:}CH{\cdot}C{:}C{\cdot}C{:}C{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	*trans*	*Coreopsis*
$H_2C{:}CH{\cdot}CH{:}CH{\cdot}C{:}C{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	10-*cis*	*Carlina*
—$C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}O{\cdot}COCH_3$	*trans*	*Coreopsis*

The matricarianol acetates have been isolated from certain members of the large genus *Aster*; they are especially abundant in *Grindelia* and *Xanthisma*. In the Compositae, the occurrence of these acetylenic alcohols seems to give clear-cut taxonomic clues. Morphologically similar species from different genera can be divided according to the type of C_{10}-acetylenes present. As an example I may mention *Erigeron peregrinus* (Pursh) Green and *E. salsuginosus* **glacialis* Gray. These are stated by most modern botanists to be closely related. Earlier botanists classified them in the genus *Aster*, but present-day authorities have transferred both to *Erigeron*. Since *E. peregrinus* contains, in all parts of the plant, *cis*,*cis*-matricaria ester together with small amounts of *cis*-lachnophyllum ester, it can be classified on a chemical basis as a genuine fleabane (*i.e. Erigeron*). *E. salsuginosus* **glacialis* contains *trans*,*trans*-matricarianol, and this only in the root, so that the chemist's answer this time is *Aster*[18].

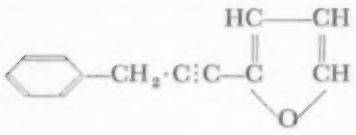
Most of the other acetylenic alcohols bear no relation to the naturally occurring acids, but are more closely related to the acetylenic hydrocarbons. This will be obvious from *Table 4*, which summarizes the remarkable results which Bohlmann[22] in Braunschweig has achieved with the " Centaur X " and " Y " compounds. These compounds were first discovered in cornflower extracts by Løfgren[23] in Stockholm. The two C_{13}-hydrocarbons had been isolated earlier by my wife from some *Coreopsis* species[21, 24]. The " 3915 "-hydrocarbon, which is found both as the *cis*- and the *trans*-isomers, is one of the most widely distributed acetylenic hydrocarbons in this plant Family, and one of those which occurs in reasonable amounts. Some species contain polar fractions which possess the same chromophore and which show peaks in the infra-red absorption spectrum which are characteristic of an acetyl group. Only once has the ester responsible been obtained pure; it is possible that higher homologues may occur in other cases, but this has not yet been proven.

VOL. 2 1961

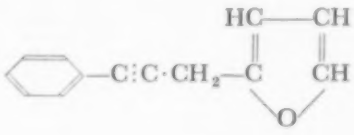
The second hydrocarbon in *Table 4* may be regarded as the parent compound of the acetate found by my wife in *Carlina vulgaris* (substitution of the methyl group), and also of the three derivatives of the C_{13}-glycol and chlorohydrin which are also shown in *Table 4*. These three chlorohydrin and α-glycol derivatives are supposed by Bohlmann to originate from epoxides. Acetylenic epoxides have so far been observed only in fungi[25]; although some evidence exists for their presence in *Achillea*, definite proof of this is still lacking[26].

Of special interest in Bohlmann's elucidation of the cornflower polyacetylenes are the 1,3-glycol derivatives in the C_{15}-class, and the C_{17}-hydrocarbons. The latter, in chain-length and unsaturation, somewhat resemble the toxins from the umbelliferous plants *Oenanthe* and *Cicuta*, the constitutions of which were elucidated by the elegant work of Lythgoe and his group in Cambridge[27].

But let us return to the alcohol which results when a hydroxyl group is introduced into the methyl group of the 1,3,11-triene-5,7,9-triyne. As the acetate, this primary alcohol was found in one of the carline thistles, *Carlina vulgaris euvulgaris* Holmboe, by my wife[20], who also established its constitution. The carline thistles are, however, the plant genus where naturally occurring acetylenes were originally found in the Compositae more than 60 years ago. Semmler isolated the main component of the essential oil of *Carlina acaulis* in 1889[28]. He named it carlina oxide, established the formula $C_{12}H_{10}O$ and restricted the constitutional possibilities to the three given:

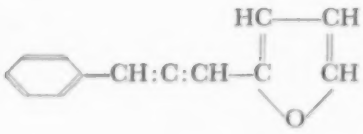


(I)



(II)

Carlina oxide

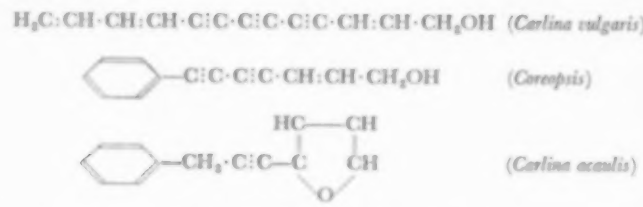


(III)

Faced with these alternatives, Semmler made the following statement: "Es ist von Hause aus sehr unwahrscheinlich, dass eine acetylenartige Verbindung vorliegt, sondern wir werden es mit der Verbindung (III) zu tun haben"; and it was not until the work of Gilman[30] in 1933, and of Pfau and his co-workers[31] in 1935, that formula (I) was proven for carlina oxide.

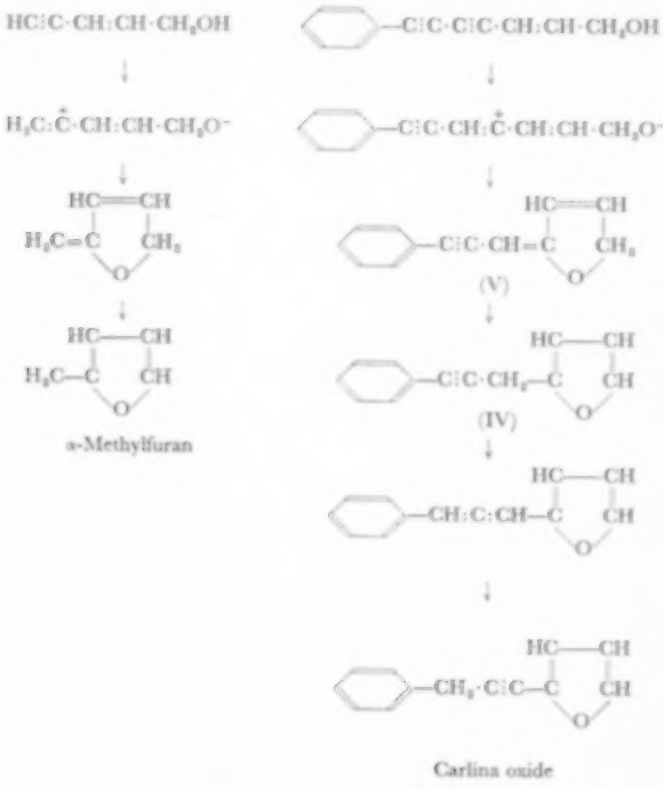
Carlina oxide, $C_{12}H_{10}O$, is isomeric with the tridecatrienetriynol isolated by my wife from *C. vulgaris*, and a third isomer is the phenylhept-

enediynol isolated as a crystalline acetate from several *Coreopsis* species by my collaborators[21]:



Jones pointed out at once that this *Coreopsis* alcohol, was, so to speak, an intermediate in the formation of carlina oxide from an aliphatic precursor.

The smooth transformation of *trans*-pentenynol with acids into α-methylfuran (see below) was realized by Heilbron[22] in 1946. The expected transformation of the *Coreopsis* alcohol into iso-carlina oxide (IV), and thence through the Semmler allene formula to carlina oxide is given by:



Unfortunately, however, all efforts by the Jones group to cyclize the *trans*-isomer of phenylheptenediynol were in vain. In his recent Pedler lecture[23],

VOL. 2 1961

Table 4. *Centaurea* acetylenes, according to Bohlmann[11]

	Constitution of Centaurea acetylenes	*Code no.*
C_{13}	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH_2$	"3915"
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH_2$	
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CHCl{\cdot}CH_2O{\cdot}COCH_3$	
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CHCl{\cdot}CH_2OH$	
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH(O{\cdot}COCH_3){\cdot}CH_2O{\cdot}COCH_3$	
C_{15}	$H_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH(O{\cdot}COCH_3){\cdot}CH_2{\cdot}$ $CH_2O{\cdot}COCH_3$	Centaur X_1(?)
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH(O{\cdot}COCH_3){\cdot}$ $CH_2{\cdot}CH_2O{\cdot}COCH_3$	Centaur X_2
C_{17}	$H_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}$ $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2$ *trans,trans* / *trans,cis*	Centaur X_3
	$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}$ $CH_2{\cdot}CH{:}CH_2$	Centaur X_4(?)

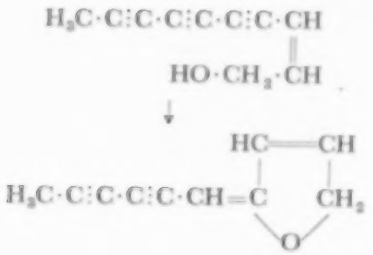
however, Jones reported that the *cis*-isomer cyclizes rapidly in weak alkali to give (V), which in weak acids rearranges to iso-carlina oxide.

This picture of the biogenesis of carlina oxide was marred by the fact that phenylheptenediynol, which can be regarded as having the dienyne residue " curled up " into a phenyl ring, had only been found in *Coreopsis* (Tribus V Heliantheae), and not in any thistle (Tribus XI Cynareae), such as carline thistle. For this reason, my wife made an investigation of another subspecies of *Carlina vulgaris*, *viz. longifolia* (Rchb) Neum., which occurs in a few localities in southern Norway. The aliphatic tridecatrienetriynol was present again, but in this subspecies the main component was a new acetylene which should have the constitution:

So far, however, our efforts to confirm this constitution by synthesis have been futile. Thus, although the *Coreopsis* alcohol could not be detected, my wife had the satisfaction of obtaining the other predictable intermediate of Semmler's carlina oxide.

In connection with the recent elegant contributions of Jones, Turner and Whiting on the cyclization of *cis*-2-enyne alcohols to dihydrofurans, which is really an approach to the solution of the problem of the formation of carlina oxide, I should like to mention the results of Christensen's work on the tiny weed *Matricaria matricarioides* (Lessing) Porter[14]. As some of you may have realized, the " rayless camomile " has invaded practically every civilized country and surrounds most chemistry departments. In the root of this plant, Christensen found a new tridecatrienediynol, as the acetate. The main component of the above-ground parts of the plant could not be crystallized, but, from the evidence of crystalline degradation products,

Christensen regards it as being the cyclization product of *cis*-dehydro-matricarianol:



The *cis*-dehydro-matricarianol has not so far been found in nature, but I should be the first to admit that this fact may be my own fault; the *trans*-isomer has been isolated by the Jones group from the fungus *Pleurotus ulmarius*[10]. Thus the formation of heterocycles seems to be just as dependent on a 2-*cis*-configuration in the enyne alcohols as in the acids.

Hydrocarbons

As to the acetylenic hydrocarbons occurring in the Compositae, I have not much to add to the review which has already been given of Bohlmann's work on the cornflower acetylenes (*Table 4*). All hydrocarbons isolated in my own laboratory are C_{13}-compounds, and are listed in *Table 5*.

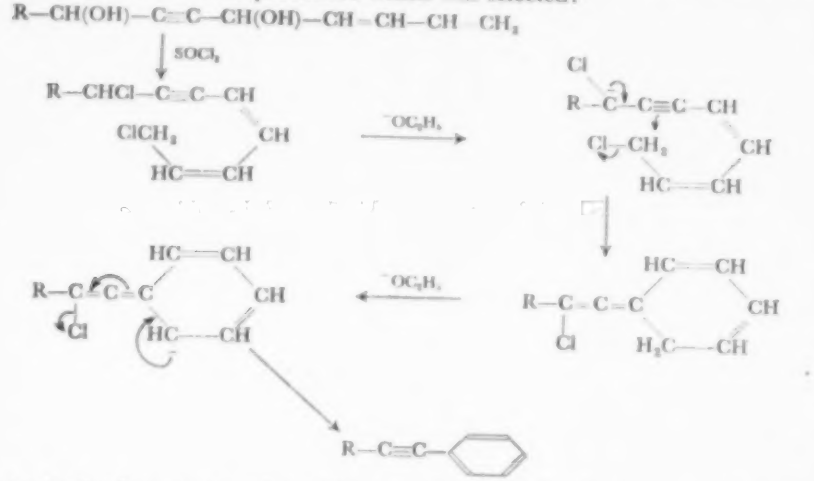
Table 5. Acetylenic hydrocarbons in Compositae (except *Centaurea*)

Constitution of acetylenic hydrocarbon	*Stereochemistry*	*Code no.*
$H_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH_2$		"4100"
$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH_2$	11-*cis* 11-*trans*	"3915"
$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH_2$	3-*cis*	
$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{-}C_6H_5$		
$H_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{-}C_6H_5$		
$H_2C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH_2$		

The structure of the "4100"-hydrocarbon, our only naturally occurring penta-acetylene so far, has been confirmed synthetically by the Jones group[35]. It forms yellow crystals which are stable for only a few minutes at room temperature. In the plant or in dilute solution the stability is surprising; it may still be found in dried plants which have been stored for months at room temperature. We have, however, never found this pentayne in any large quantity. It has been isolated in the solid state from about a dozen plants; in the numerous other cases where the very characteristic spectrum has been encountered, there is no proof that the enepentayne chromophore is not present in a longer aliphatic chain.

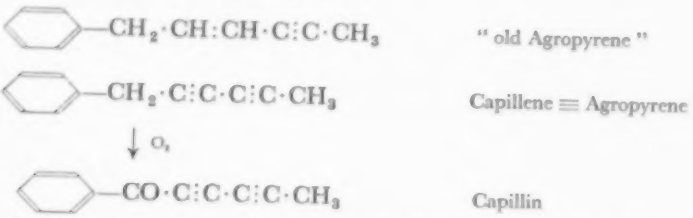
VOL. 2 1961

Two of our hydrocarbons contain the phenyl residue, the first one bearing just the same relation to the foregoing aliphatic compound as the *Carlina vulgaris* alcohol to the *Coreopsis* alcohol. Without delving into the fascinating question of whether Compositae are able to transform a dienyne chain directly into a benzene ring, or whether both originate from a common oxygen-containing precursor. I should like to mention that, when Skattebøl and Sørensen[37] tried to synthesize the aliphatic trideca-1,3,11-triene-5,7,9-triyne, he obtained the phenylhept-5-ene-1,3-diyne as the main reaction product. The procedure which was selected:



is a standard route to polyacetylenes, and the cyclization seems to be a general reaction when the molecule contains a terminal butadienyl residue.

Beside carlina oxide itself, the capillene-agropyrene series constitute the classical phenylacetylenes of the Compositae. The constitutions of the three members known are given by:



and their somewhat confused history may be summarized as follows. In 1922 Schimmel & Co.[38] prepared a sample of the essential oil of couch-grass, *Agropyron repens* (L.) PB. This oil was investigated by Treibs in 1944, and the main compound was stated by him to have the constitution which I have named " old agropyrene "[39]. Meanwhile, early in 1920, Japanese chemists started work on the essential oil of the fungicidal mugwort *Artemisia capillaris*. In 1930, Arima and Okamoto[40] isolated a hydrocarbon " capillene " from this source and formulated it as $C_{13}H_{14}$. In 1954 this hydrocarbon was again isolated, by Harada[41], who proposed a C_{12}-formula.

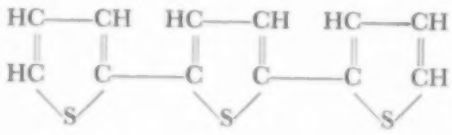
Harada at first supposed capillene to be an isomer of " old agropyrene ", but, in a 1957 paper[42], he corrected the formula to $C_{12}H_{10}$ and proved the structure given for capillene by synthesis. During the same period, Imai[43] and his collaborators isolated the fungicidal principle of *A. capillaris*. This they named capillin, and again the structure was confirmed by synthesis. In the meantime (1954), Cymerman-Craig[44] had synthesized the *trans*-isomers of " old agropyrene ", and the properties of the synthetic compound indicated that the couch-grass compound could hardly have the constitution indicated by Treibs. In collaboration with Treibs, Cymerman-Craig in 1959 proved the identity of capillene and the couch-grass acetylene, and at the same time demonstrated the smooth autoxidation of capillene into capillin.

The reason that " old agropyrene " has not been omitted from the list is a paper published in 1958 by Goljmov and Afanesev[46]. These authors isolated from the Russian mugwort, *Artemisia scoparia*, two hydrocarbons: one, $C_{12}H_{10}$, which was identical with capillene; the other, $C_{12}H_{12}$, which was stated to have the formula of " old agropyrene ". An interesting point is that so far no C_{12}-aliphatic acetylene has been isolated from a mugwort. The only C_{12}-compound known from botanically related plants is a mono-thiophene, possibly derived from a parent hydrocarbon $C_{12}H_8$.

VOL
2
1961

Thiophenes

The thiophenic acetylenes discovered in recent years appear to constitute one of the largest groups of naturally occurring acetylenes. The isolation, by Zechmeister and Sease in 1947, of terthienyl from a special variety of the African Marigold, *Tagetes erecta*, provided the first representative of this class:



Terthienyl itself apparently has no relation at all to aliphatic acetylenes. It is, however, noteworthy that Challenger and Holmes[48] suggested in 1953 that there should be a connection between the occurrence of aliphatic polyacetylenes and terthienyl in the same plant Family. That these relationships might, in some cases, be rather simple was shown, originally, more-or-less by accident. *Coreopsis grandiflora* Hogg ex Sweet gives an essential oil with an ultra-violet absorption spectrum which is completely dominated by the elegant spectrum of phenylheptatriyne (*Figure 2*). The phenylheptatriyne also possesses an unusually marked tendency to crystallize. On one occasion, my wife was chromatographing the oil and, as a matter of routine, she took the usual cuts in the eluent and obtained one crystalline fraction after the other. The melting points of the crystals from the later fractions were lower by a few degrees, and, fortunately, my wife determinated their ultra-violet absorption spectra. That of the material from the later fractions is given by curve A in *Figure 3*. Curve B shows the spectrum of its tetrahydro-compound. The infra-red absorption

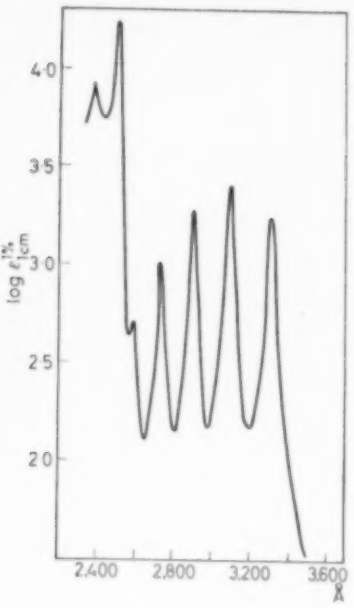


Figure 2. Ultra-violet light absorption spectrum of phenylheptatriyne

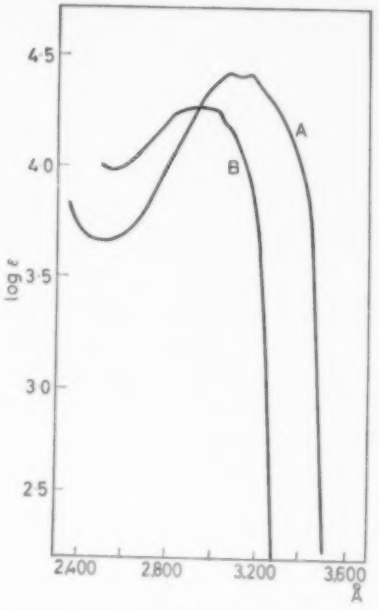
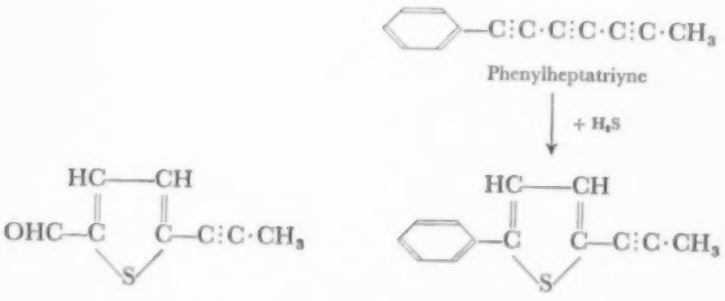
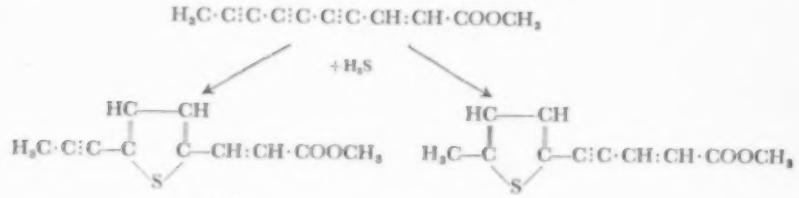


Figure 3. Ultra-violet light absorption spectra in hexane of: A. 2-phenyl-5-(1-propynyl)-thiophene; B. 2-phenyl-5-(n-propyl)-thiophene

spectrum revealed a monosubstituted phenyl residue, and a comparison with the curve that had just been published by Birkinshaw[50] for junipal, 5-(1-propynyl)-2-formylthiophene, indicated that there might also be a 2,5-disubstituted thiophene present. Due to the work of Birkinshaw on junipal, one of the odoriferous principles of the Basidiomycete, *Daedelia iuniperina*, the rest of the constitutional work was easy: the compound was proved to be 2-phenyl-5-(1-propynyl)-thiophene. The formal relationship between phenylheptatriyne, 2-phenyl-5-(1-propynyl)-thiophene and junipal is shown as follows:



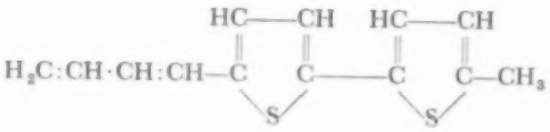
Dehydro-matricaria ester is formally related to two isomeric thiophenes, thus:



(VI)

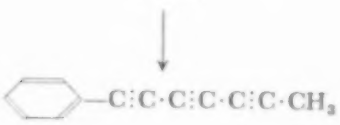
Guddal has demonstrated that two crystalline compounds in the root of tansy, *Chrysanthemum vulgare* Bernh., are the *cis*-and *trans*-isomers of one of these thiophenes (VI). By synthesis of the *trans*-isomer, Skattebøl has confirmed this constitution[52]; the junipal of Birkinshaw was an intermediate in this synthesis.

Another interesting member was isolated by Mrs Liaaen Jensen[53] from some *Bidens* species, *viz.* 5-methyl-5′-butadienyl-2,2′-dithienyl (VII). This was the first naturally occurring derivative of dithienyl to be discovered, and in this case also the constitution was confirmed synthetically by Skattebøl. The 5-methyl-5′-butadienyl-2,2′-dithienyl can be formally derived from the trideca-1,3-diene-5,7,9,11-tetrayne (VIII), which can also be regarded as the hypothetical precursor of the phenylheptatriyne found in a number of *Bidens* species:



(VII)

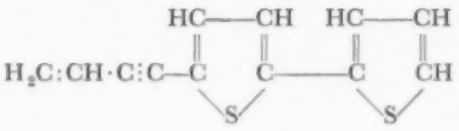
(VIII)



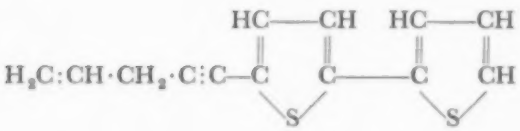
However, trideca-1,3-diene-5,7,9,11-tetrayne (VIII), which is a positional isomer of the " 3915 "-hydrocarbon, has not so far been isolated from plants.

VOL. 2 1961

In 1959, Uehlenbrook[54] and his collaborators in the research laboratory of Philips-Roxane demonstrated that the terthienyl of Zechmeister was one of the nematodicidal principles of extracts from *Tagetes* roots. More potent, however, than terthienyl was a liquid compound with a broad ultra-violet light absorption maximum at 3400 Å. These Dutch chemists gave this nematodicidal principle the structure (IX). Fractions with similar ultra-violet and infra-red light absorption spectra had been isolated



(IX)

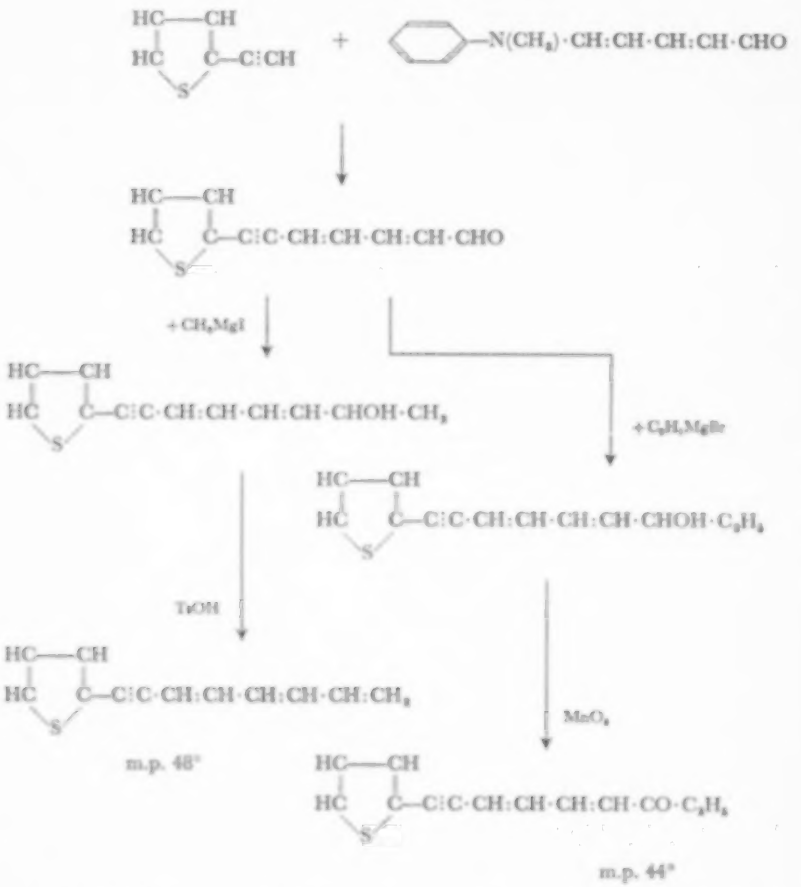


(X)

by my collaborators from the thistles *Berkheya macrocephala* and *Echinops sphaereocephalus*. Since these fractions possessed an ultra-violet light absorption maximum at a shorter wave-length than that of 5-methyl-5′-butadienyl-2,2′-dithienyl (VIII), but which is in good agreement with those of the monoethylene and monoacetylene derivatives of 2,2′-dithienyl, we favoured the C_{13}-structure (X) for the constituent of these fractions. Although some uncertainties thus remain as to the constitution of the nematodicidal principle of *Tagetes*, this compound and the 5-methyl-5′-butadienyl-2,2′-dithienyl (VII) obviously provide intermediates which would encourage not only Professor Challenger, but also any other chemist, to postulate connections between aliphatic polyacetylenes and naturally occurring thiophenes.

Finally the scentless mayweed, with which my small group originally started work in the acetylene field, has also furnished some new thiophenes[55]. In our 13th communication in 1954[8], reporting the isolation of *trans*-dehydromatricaria ester from members of the subgenus *Tripleurospermum* of Schulz-Bipontinus, Miss Holme and my wife described two crystalline compounds which, at that time, were characterized only by melting-point and ultra-violet light absorption spectra. When the work was resumed, my wife found a number of thiophenic compounds of which five have now been isolated in a pure state: one turned out to be identical with the *trans*-isomer of methyl-5-propynyl-2-thienylacrylate which had been isolated earlier by Guddal from tansy. The four others are new ones, and all are mono-substituted thiophenes. The synthesis of two of them with the aid of the

Jutz synthesis[56], one of the most elegant recent contributions to the synthesis of acetylenic compounds, is represented as follows:

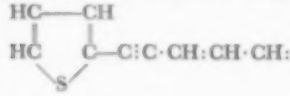
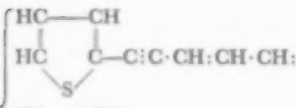
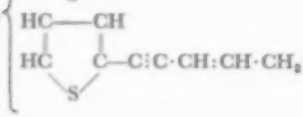


The third of the new thiophenes from scentless mayweed might be the α,β-dihydro-derivative of the ketone. These new monosubstituted thiophenes bear interesting relationships to the acetylenes isolated earlier from *Matricaria* and the closely related mugworts (*Artemisia*). As will be obvious from *Table 6*, the monothiophenes may well be connected with the Centaur X_3 and the C_{14}-ketone of these species, by ω-oxidation and subsequent decarboxylation. The studies in Oxford on some aliphatic polyacetylenes of certain fungi have already made such ω-demethylations plausible[57].

These new members of the acetylene family present in scentless mayweed raise once again the question of whether or not these short-chain polyacetylenes originate as degradation products of unsaturated fatty acids. Bohlmann has discussed this problem in connection with his cornflower series, as has E. R. H. Jones on the basis of his fifty or so polyacetylenes from

VOL. 2 1961

Table 6. Related compounds in the Tribus Anthemideae, subtribus Anthemidineae

	Chemical constitution	*Stereochemistry*	*Source*
C_{17}	$H_3C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2$ (Centaur X_4)		*Artemisia (Matricaria)*
C_{14}	$H_3C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3$		*Artemisia (Matricaria)*
C_{10}	$H_3C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}COOCH_3$	*cis-*, *trans-*	*Artemisia*, *Matricaria*
	$H_3C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{:}CH{\cdot}COOCH_3$	*2-cis,8-cis-*, *2-trans,8-cis-*	*Matricaria*
	$H_3C{\cdot}CH{:}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}CH_2{\cdot}COOCH_3$	*8-cis-*	*Matricaria*
C_{12}			*Matricaria inodora*
C_{13}			*Matricaria inodora*
			*Matricaria inodora*

fungi. The answer is up to the biochemist: it is his privilege and his responsibility. The organic chemist will, from my experience, have his hands full with the isolation of numerous new members of the known structural groups of naturally occurring acetylenes, and, without doubt, with the elucidation of the structures of quite new types.

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VOL.
2
1961

CHEMISTRY AND BIOCHEMISTRY OF SOME BIOLOGICALLY ACTIVE BACTERIAL LIPIDS

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INTRODUCTION

Work, which was begun in the author's laboratory in 1948, on the chemistry of various lipid fractions of Mycobacteria and other acid-fast micro-organisms, has led to the identification and elucidation of the chemistry of a number of compounds having unusual structures and interesting biological activities. The principal compounds studied are branched-chain high molecular weight fatty acids, glycolipids and peptido-glycolipids. Some information on biosynthetic mechanisms in these series has also been obtained.

The infection of a healthy animal or human being by tubercle bacilli gives rise to several pathological manifestations, such as: (i) formation of tubercles; (ii) establishment of a delayed type of hypersensitivity; (iii) loss of weight, haemorrhages, and death, due to the presence of a toxic factor; (iv) increased production of antibodies; (v) development of resistance to a second infection.

We shall see that all of these pathological phenomena are due to particular lipid fractions of the tubercle bacillus. Besides these, we shall consider also a new category of glycolipids which are typical for certain strains of Mycobacteria (see *Table 1*).

Table 1. Correlation of biological activity and chemical structure

Pathological phenomenon	*Chemical structure of the corresponding lipid*
Formation of tubercles	Branched-chain fatty acids
Delayed hypersensitivity	Esters of mycolic acids with carbohydrates
Loss of weight, haemorrhages, death	Cord factor (6,6′-dimycoloyl-trehalose)
Increased production of antibodies	Wax D of human strains (a peptido-glycolipid)
Resistance to infection	Phosphoglycolipids (?)
Specific pathogenicity (?)	Mycoside A and B (glycolipids) Mycoside C (a peptido-glycolipid)

TUBERCLE FORMATION

Branched-chain fatty acids

Branched-chain fatty acids and their derivatives seem to be the principal compounds producing the characteristic tubercles observed in tuberculosis.

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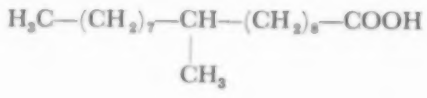
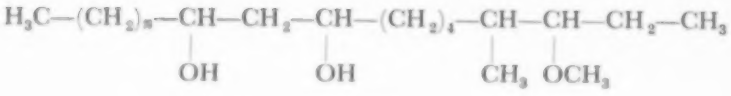
The excellent work of Anderson[1], published between 1926 and 1946, has shown that Mycobacteria contain several branched-chain fatty acids. One can distinguish two large groups: (i) compounds having only methyl branchings; (ii) compounds with longer branched chains.

Compounds with methyl side-chains

In this group, we find compounds having only one methyl side-chain, such as tuberculostearic acid (I) and phthiocerol (II)[2], and those having several methyl branchings, such as phthienoic acid (III)[3] and mycocerosic acid (IV)[4].



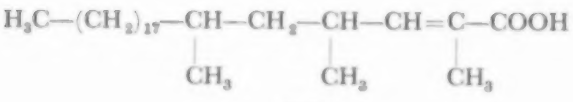
(I)



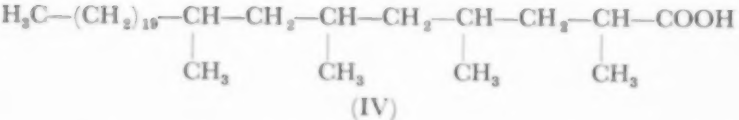
(II)

(a) $n = 20$

(b) $n = 22$



(III)



(IV)

It seems that compounds having only one methyl branching, such as (I) and (II), are devoid of biological activity, whereas those with three or more methyl branchings, such as (III) and (IV), are potent producers of tubercles (see the review by Asselineau[5]).

The structural determination of phthienoic and mycocerosic acids is due to Polgar, Cason, J. and C. Asselineau, and S. and E. Stenhagen, and cannot be described in detail here (for recent reviews, see refs. 6 and 7).

Two different mechanisms of biosynthesis can be considered for the fatty acids with methyl side-chains: the " Birch mechanism "[8], consisting of the fixation of a methyl group (from methionine) onto a polyacetic acid chain*

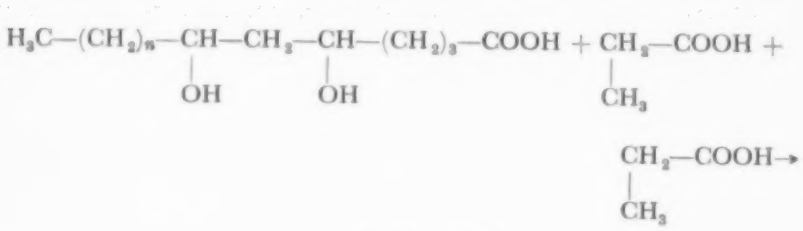
* Hofman and Liu[9] have shown that the cyclopropane ring of lactobacillic acid is formed *in vivo* by the fixation of a one carbon unit derived from formate onto *cis*-vaccenic acid; the fixation of methyl groups on aliphatic chains by this mechanism does not seem to have been observed yet.

VOL. 2 1961

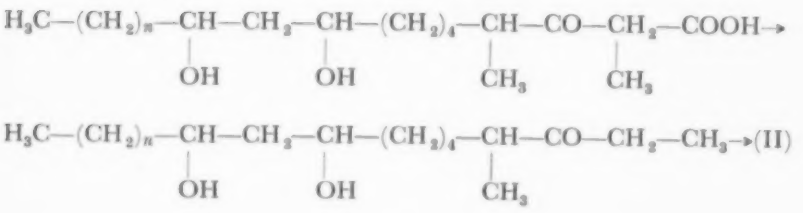
and the " propionic acid mechanism ", consisting of the condensation of a normal fatty acid in the α-position of one molecule of propionic acid. Repetition of the condensation of propionic acid could give molecules such as (III) and (IV). This mechanism had been considered by Polgar and Robinson[10], Robinson [11], Woodward[12], and Gerzon *et al.*[13], and has been recently proven in its simplest form for the biosynthesis of α-methylbutyric acid in the *Ascaris*[14] and for the formation of the branched chain of the antibiotic erythromycin[15, 16].

Recent experiments of Gastambide and Grisebach (unpublished) have shown that propionic acid, when incubated with growing cultures of the non-virulent human strain *H37Ra*, is incorporated in good yield into mycocerosic acid (IV).

For phthiocerol, which has been shown to be a mixture of two homologous glycols (IIa) and (IIb)[2], the following biosynthetic route can be postulated:



$n = 20$ or 22



(V)

The dihydroxy-keto compound (V) has been isolated as one of the " companions " of phthiocerol and has been named phthiodolone[17].

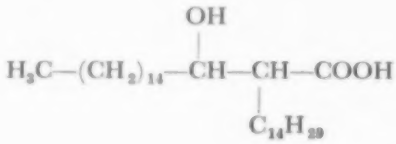
Compounds with long side-chains

These are the so-called mycolic acids: the latter have been defined as " high molecular weight β-hydroxy acids with a long side-chain in α "[18].

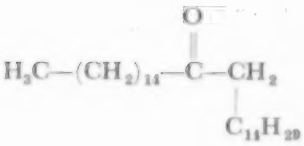
Three principal groups of mycolic acids have been described so far: (i) corynomycolic acid[19] and corynomycolenic acid[20], of *Corynebacterium diphtheriae*, with 32 carbon atoms; (ii) the nocardic acids, of *Nocardia asteroïdes*, with 50 ± 3 carbon atoms[21]; (iii) the mycolic acids of Mycobacteria, with more than 80 carbon atoms[1, 6, 22].

We have studied in detail the biosynthesis of the simplest of these acids, corynomycolic acid; this compound, $C_{32}H_{64}O_3$, m.p. 70°, $[\alpha]_D = +7{\cdot}5°$,

has been isolated from the lipids of *C. diphtheriae* and *C. ovis*. Its structure (VI) has been established by degradation[19] and confirmed by synthesis[23].



(VI)



(VII)

The presence of free palmitic acid and of palmitone in the lipids of *C. diphtheriae*[25], as well as previous work on the mycolic acids of Mycobacteria, suggested that corynomycolic acid is formed *in vivo* by the condensation of two molecules of palmitic acid (probably as palmitoyl-coenzyme A) and reduction of the intermediate β-ketoester. Palmitone (VII) could be formed through saponification and decarboxylation of the β-ketoester.

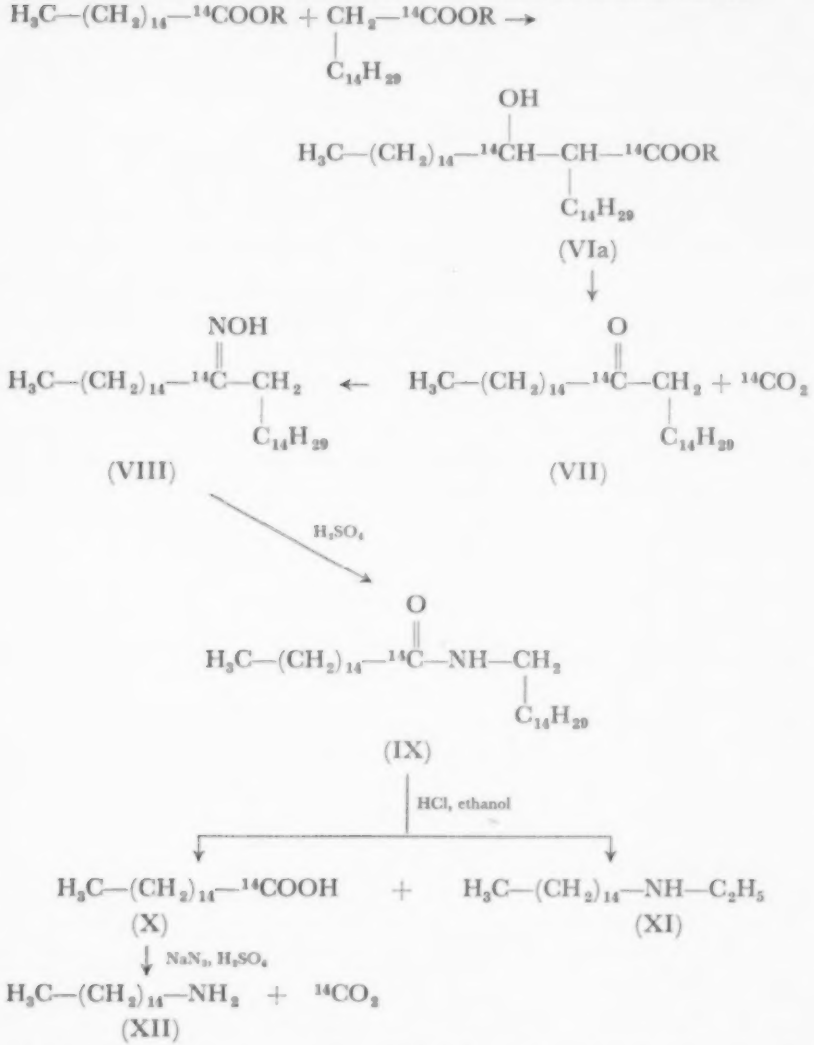
Recent experiments of Gastambide-Odier[24] with 1-^{14}C-palmitic acid have confirmed this hypothesis, and have shown that corynomycolic acid is, in fact, formed *in vivo* by the condensation of two molecules of palmitic acid.

Cultures of diphtheria bacilli (*C. diphtheriae*, strain Parke-Williams 8) were grown on Loiseau-Philippe medium containing 10 μc of the potassium salt of 1-^{14}C-palmitic acid (specific activity $(43{\cdot}1 \pm 6{\cdot}0) \times 10^7$ counts min^{-1} mmole^{-1}). After 12 days at 37°, the cells were centrifuged, washed, and extracted with alcohol–ether (1:1).

Corynomycolic acid was isolated in a pure state by chromatography on magnesium silicate–celite, esterification, distillation under reduced pressure, and finally chromatography of the methyl ester on alumina; after several subsequent stages of purification, 0·4 mg of pure methyl corynomycolate (m.p. 59–62·5° and specific activity $44{\cdot}7 \times 10^6$ counts min^{-1} mmole^{-1}) were isolated. This represents about 3 per cent of the total radioactivity added with the potassium palmitate.

If corynomycolic acid is synthesized *in vivo* from two molecules of palmitic acid, then, in these experiments with carboxyl-labelled palmitic acid, only the C–1 and C–3 atoms should be labelled, and each should contain half of the radioactivity. This was proved to be the case experimentally, the reactions involved being represented schematically as follows:

VOL. 2 1961



The radioactive corynomycolic acid (VIa) was first diluted with authentic corynomycolic acid to a specific activity of $(33{\cdot}0 \pm 4{\cdot}0) \times 10^4$ counts mg^{-1} min^{-1} $mmole^{-1}$, and then oxidized and decarboxylated in a chromic acid–acetic acid mixture. The barium carbonate obtained had a specific activity of $(16{\cdot}3 \pm 6{\cdot}4) \times 10^4$ counts min^{-1} $mmole^{-1}$, and the palmitone (VII) obtained in a pure state (m.p. 79–80·5°) had the same specific activity ($(16{\cdot}3 \pm 2{\cdot}3) \times 10^4$). This already shows that the carboxyl of the labelled corynomycolic acid has half the radioactivity of the whole molecule.

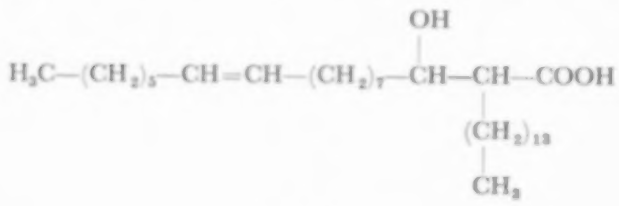
The radioactive palmitone (VII) was then degraded in the following way: the oxime (VIII) was prepared and rearranged to the amide (IX); this was cleaved in acid medium and gave an inactive amine (XI) and palmitic

acid (X) having the same specific activity ($(12{\cdot}5 \pm 3{\cdot}4) \times 10^4$) as the palmitone; decarboxylation of this palmitic acid then gave again an inactive amine (XII) and barium carbonate having the same radioactivity as the initial sample of palmitone (VII).

This proves that, in the corynomycolic acid formed *in vivo* in the presence of 1-^{14}C-palmitic acid, only the C–1 and C–3 atoms are radioactive; this can only be explained by the condensation of two intact molecules of palmitic acid; otherwise, if the palmitic acid had undergone an initial degradation, radioactivity would have been " smeared out " over the whole molecule.

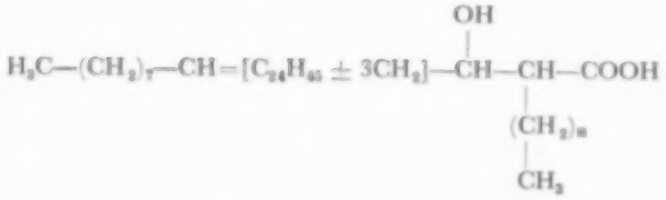
It can be surmised that one of the molecules of palmitoyl-CoA has to be carboxylated to tetradecylmalonyl-CoA. The detailed mechanism of the condensation reaction has not yet been studied.

Corynomycolenic acid (XIII), the second C_{32}-mycolic acid isolated from *C. diphtheriae*[20], is obviously formed from one molecule of palmitoleic acid, $CH_3-(CH_2)_5-CH=CH-(CH_2)_7-COOH$ (which also exists in large quantities in the free state in the diphtheria bacillus), and one molecule of palmitic acid. Here, an intermediary β-keto-ester could give a ketone, Δ^7-palmitenone, $CH_3-(CH_2)_5-CH=CH-(CH_2)_7-COC_{15}H_{31}$, on saponification; this has also been isolated from the lipids of *C. diphtheriae*[25].



(XIII)

The nocardic acids, $C_{56}H_{96}O_3 \pm 3CH_2$, have been isolated recently from the pathogenic Actinomycete *Nocardia asteroïdes*, and the partial structure (XIV) established (Michel *et al.*[21]); they are probably synthesized *in vivo* by the condensation of three molecules of long chain (C_{18}?) acids in a similar way.

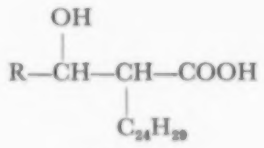


(XIV)

(a) $n = 11$

(b) $n = 13$

Mycolic acids are typical constituents of Mycobacteria, and were discovered in 1938 by Lesuk and Anderson[26]. Detailed studies of their chemical structure, pursued in our laboratory principally by J. Asselineau, have yielded the following results: mycolic acids of human and bovine strains of *M. tuberculosis* have the approximate formula $C_{88}H_{176}O_4 \pm 5\ CH_2$ and the general structure (XV):



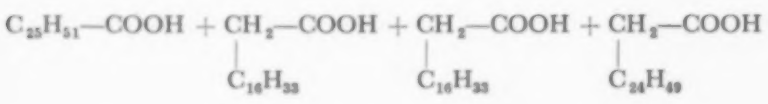
(XV)

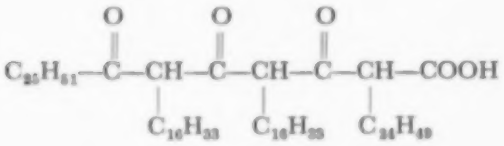
where R is a radical containing about 60 carbon atoms with one oxygen function (OH, or OCH_3 or a carbonyl) and three chains.

Extensive degradative evidence has shown that in some of these mycolic acids the second oxygen function is either on C–5 or further away from the carboxyl, and that C–4 or probably C–4 and C–6 carry side-chains[6, 22].

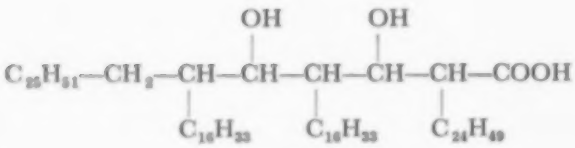
As to the length of the various side chains, it is known that at least one of these (besides that at C–α) has 24 to 26 carbon atoms, and that the others are shorter (C_{16} to C_{18}).

All experimental evidence is in agreement with formulae (XVII) and (XVIII), which could result from the condensation of four molecules of long-chain fatty acids ($2 \times 26 + 2 \times 18 = 88$) by the mechanism which we have proven for corynomycolic acid. An appropriate reduction of the intermediate (quite hypothetical) triketo-compound (XVI) gives the two types of mycolic acids (XVII) and (XVIII). These structures are in agreement with all experimental findings[27].

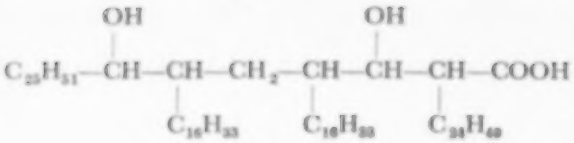




(XVI)



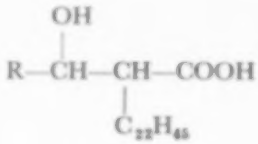
(XVII)



(XVIII)

The mycolonic acids[28] (some of which are 3-hydroxy-5-keto-compounds) can be considered as intermediates in this reduction.

Avian and saprophytic strains of Mycobacteria are incapable of synthesizing hexacosanoic acid; their longest chain free fatty acid is tetracosanoic acid; the mycolic acids of these strains have the general structure (XIX)[29]:



(XIX)

where R is a radical $C_{28}H_{116} \pm 3CH_2$ with one hydroxyl group.

It may be mentioned also that Karlsson[29] has found mutants of Mycobacteria for which hexacosanoic acid acts as growth factor; it seems obvious that this latter acid is indispensable as starting material for the synthesis of mycolic acids.

We may sum up the actual knowledge of the biosynthesis of branched-chain compounds by Mycobacteria and Actinomycetes in general as follows: the condensation of a straight-chain (usually even-numbered) acid R′—COOH on the C-α atom of an acid R″—CH_2—COOH gives methyl-branched fatty acids when R″ is methyl, and gives mycolic acids when R″ is a longer alkyl group.

Analogously to the biosynthesis of straight-chain fatty acids, these condensations can give β-hydroxy-acids R′—CHOH—CHR″—COOH, which can be dehydrated to α,β-unsaturated acids R′—CH=CR″—COOH and reduced to saturated acids R′—CH_2—CHR″—COOH. Examples of one or the other of these three stages can be found in many bacterial lipids*.

It is interesting that each mechanism of biosynthesis of fatty acids in acid-fast bacteria seems to have an optimum range of molecular size:

* In the *Ascaris* all three stages have been found, *e.g.*: CH_3—CH(OH)—CH(CH_3)—COOH, CH_2=C(CH_3)—CH=CH—COOH and CH_3—CH_2—CH(CH_3)—COOH (Saz and Weil[14], and personal communication from Professor Bueding).

normal fatty acid synthesis stops at C_{26}, branched acids with several methyl groups have 21 to 34 carbon atoms, whereas mycolic acids have 32 to 88 carbon atoms.

Mycolic acids, as well as their esters with carbohydrates, are potent producers of tubercles *in vivo*[5]; we shall see that glycolipids and peptido-glycolipids containing 50–88 per cent mycolic acid have other interesting biological activities.

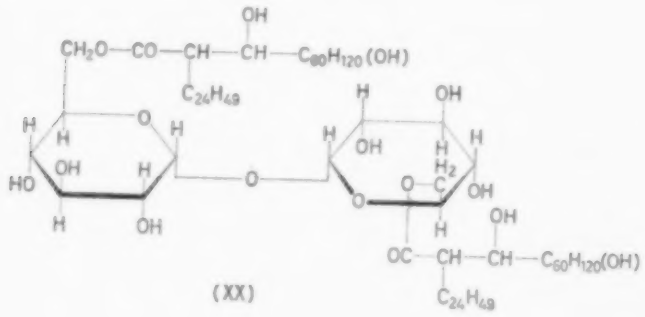
DELAYED TYPE OF HYPERSENSITIVITY

The injection of tuberculin, a protein (or mixture of proteins) secreted by the tubercle bacillus into the culture filtrate, is not sufficient to produce the typical " tuberculin hypersensitivity ". Raffel[31] has shown that one can elicit this hypersensitivity by simultaneous injection of tuberculin and a purified wax fraction. It was later found that all esters of mycolic acid with carbohydrates are active[32].

Amongst the lipids produced by tubercle bacilli, a particular wax fraction, called wax D, is also active in this respect. We shall say more about this fraction later.

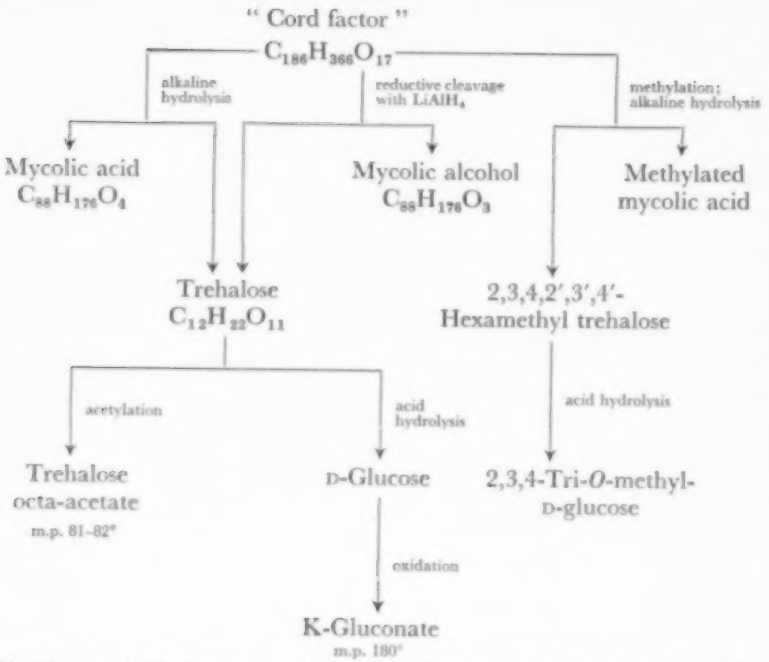
THE TOXIC FACTOR

The toxic factor has been called " cord factor ", because it is found in " cord forming " organisms, i.e. virulent and attenuated strains which grow in the culture medium in " serpentine cords "[33]. One intravenous injection of 20μg of natural cord factor kills mice within 10–20 days; haemorrhages in the lung are the principal lesions observed.

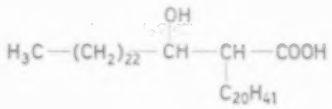


(XX)

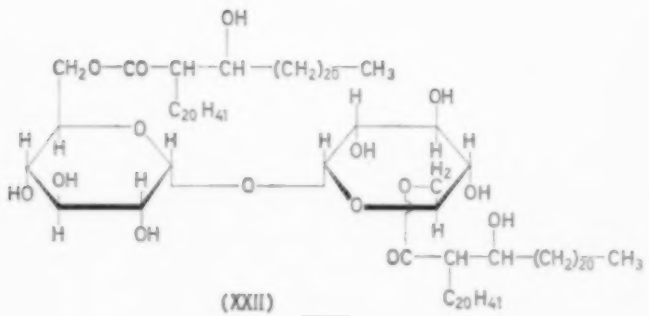
Cord factor has been isolated in a pure state after repeated chromatographic purifications on magnesium silicate and silicic acid, and its structure as the 6,6′-dimycolate of trehalose (XX) ($C_{186}H_{366}O_{17} \pm 10\ CH_2$) established by degradation[34], and by synthesis[35, 36], starting from trehalose and natural mycolic acids.



Simple, synthetic mycolic acids, such as (XXI) obtained by condensation of two molecules of methyl docosanoate, have also been esterified with trehalose and have yielded " small cord factors ", *e.g.* (XXII) ($C_{100}H_{194}O_{15}$)[36] which show approximately the same biological activity as natural cord factor.



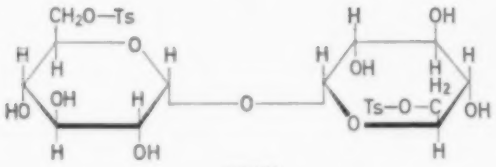
(XXI)



(XXII)

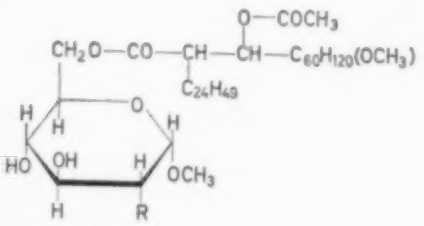
VOL. 2 1961

The most specific method of obtaining 6,6′-diesters of trehalose is to heat 6,6′-ditosyl trehalose (XXIII), with two molecules of the potassium salt of an acid[37].



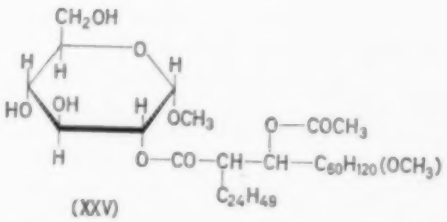
(XXIII)

Concerning the relation between chemical structure and cord factor activity, the following preliminary statements have been made[38] on the basis of unpublished experiments by Bloch with compounds prepared in the author's laboratory: 6-mycolates of monoses (D-glucose, D-galactose, D-glucosamine, *e.g.* (XXIVa, b)) are toxic, but to a lesser degree than trehalose esters; the corresponding 2-mycolates (XXV) and mycolamides (XXVI) are not toxic.

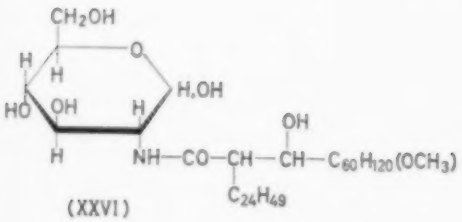


(a)R = OH
(b)R = NH—COCH$_3$

(XXIV)



(XXV)



(XXVI)

The 6,6′-dimycolates of trehalose seem more active than the 6-mono- or 2,6,6′-trimycolates.

Acetylation of the β-hydroxyl of mycolic acid diminishes only slightly the activity of cord factor; fully acetylated cord factor is inactive.

The influence of the structure of the acid esterifying trehalose can be characterized as follows: even behenic (docosanoic) esters of trehalose are active, but doses larger than 0·1 mg are necessary. The 6,6′-diester of trehalose with the synthetic mycolic acid $C_{44}H_{88}O_3$ (XXI) has about 50 per cent of the activity of natural cord factor. Dehydration of the latter acid gives the unsaturated acid (XXVII):

$$H_3C-(CH_2)_{20}-CH=\underset{\displaystyle C_{20}H_{41}}{\overset{\displaystyle |}{C}}-COOH$$

(XXVII)

which, as the 6,6′-diester of trehalose, is inactive at 0·1 mg dose levels.

Concerning the mechanism of action of cord factor, Kato *et al.*[40] have found that injection of cord factor decreases the activity of most DPN-linked dehydrogenases.

For reviews on cord factor, see Lederer[38] and Noll[39].

VOL. 2 1961

INCREASED PRODUCTION OF ANTIBODIES

Freund's adjuvant, consisting of a water-in-oil emulsion containing killed Mycobacteria in the oil phase and the antigen in the aqueous phase, has been widely used by immunologists for increasing antibody production in animals. Freund[41] has reviewed our knowledge of the mode of action of this type of adjuvant.

After the preliminary experiments of White *et al.*[42] with a " purified wax fraction ", we showed with White *et al.*[43] that a particular wax fraction of human strains of *M. tuberculosis* can effectively replace the whole bacilli in Freund's adjuvant mixture.

This wax fraction, which we call *wax D*[5–7], is extracted from the bacilli with chloroform and can be separated from other wax fractions as a result of its insolubility in boiling acetone.

The wax D fractions of human strains of tubercle bacilli are high-melting dextrorotatory solids which represent 6–8 per cent of the dry weight of virulent strains, but only about 2 per cent of non-virulent strains[44].

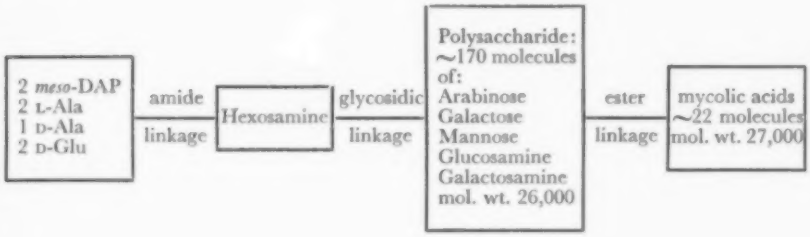
A recent study[45] of the chemical structure of wax D has shown that it is a high molecular weight lipid, and that the composition and molecular weight varies from strain to strain. The best analysed wax D fraction, that of the human virulent strain " Brévannes ", has a molecular weight of about 54,000. On saponification, about 50 per cent of mycolic acid $C_{88}H_{176}O_4$ is obtained (corresponding to approximately 22 molecules) and 50 per cent of a water-soluble portion. This latter is a peptido-muco-polysaccharide and seems to be homogeneous on ultracentrifugation and by immunological reactions.

The carbohydrate moiety of this peptido-mucopolysaccharide contains the following sugars: D-arabinose, D-mannose, D-galactose, glucosamine and galactosamine*; traces of muramic acid are present, probably as an impurity.

The peptide moiety of wax D of human strains is of particular interest, because the analogous wax D fractions of bovine and saprophytic strains, which are nitrogen-free glycolipids, are inactive as adjuvants; thus, the peptide moiety seems to play a definite rôle in the adjuvant activity of wax D[43].

It had already been found several years ago that wax D fractions of all human strains investigated contain the same three amino-acids: *meso*-diaminopimelic acid, glutamic acid and alanine[6].

The particular wax D of the strain " Brévannes " which was studied in detail contains two molecules of *meso*-diaminopimelic acid (DAP), two molecules of D-glutamic acid (Glu) and three molecules of alanine (Ala), one of which is D. The presence of several amino-acids of " unnatural " configuration is quite remarkable. A tentative structure for wax D of the human virulent strain " Brévannes " of *M. tuberculosis* has been proposed[45] as follows:



Quite recently, it has been shown that these seven molecules of amino-acids form a heptapeptide, and the sequence of amino-acids in this heptapeptide has been established as: *meso*-DAP.D-Ala.D-Glu.D-Glu.L-Ala.*meso*-DAP.L-Ala[47].

From the products of the partial acid hydrolysis of the water-soluble part of wax D, a compound was isolated containing one molecule of *meso*-DAP, one of galactosamine and one of arabinose. Galactosamine was found to be linked to a carboxyl-group of *meso*-DAP. This shows that the heptapeptide is linked by a carboxyl from one of its *meso*-DAP molecules to galactosamine, which is itself joined by a glycosidic linkage with arabinose, one of the components of the polysaccharide moiety. A second linkage probably exists between one carboxyl-group of D-glutamic acid and arabinose[47].

It should be mentioned that delipidated bacterial residues of human, bovine, avian and saprophytic strains are also active adjuvants; this can be explained by the fact that these residues contain essentially cell-walls. It is

* The optical configuration of these amino-sugars has not yet been determined; however, Haworth *et al.*[46] have found D-glucosamine in a " lipid-bound " polysaccharide of *M. tuberculosis* closely related to the polysaccharide of wax D.

known that mycobacterial cell-walls are mainly composed of three amino-acids (alanine, glutamic acid, and α,ε-diaminopimelic acid) linked to a polysaccharide containing arabinose, mannose, galactose and muramic acid[48]. They thus have an overall composition very similar to that of the water-soluble part of wax D of human strains.

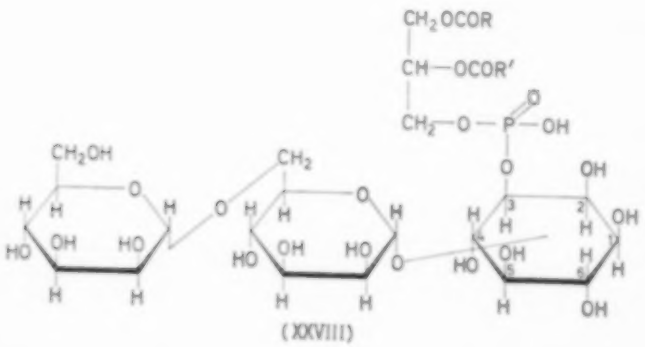
The adjuvant activity of wax D of the human strain of *M. tuberculosis* is probably due to its general chemical analogy with the cell-wall, and one might consider the cellular reactions which result in the increase of antibody production as a general reaction of the tissues of the higher organism to contact with mycobacterial cell-walls.

DEVELOPMENT OF RESISTANCE TO INFECTION

Boquet and Nègre[49, 50] of the Pasteur Institute, Paris, have shown long ago that methanol extraction of acetone-defatted tubercle bacilli yields an extract which possesses immunizing properties. They had called this crude fraction " antigène méthylique ", and Macheboeuf *et al.*[51] had shown that phospholipids are the main antigenic components of this extract.

More recently, Weiss and Dubos[52] have confirmed the findings of Boquet and Nègre[49], and have studied the preparation of active extracts and some biological aspects of immunization.

VOL. 2 1961



(XXVIII)

In view of the interesting biological properties of the crude phospholipid fraction, we have undertaken a more detailed study of its constituents.

It was already known from the work of Anderson[1] that mycobacterial phospholipids contain inositol and mannose. We have found with Mrs Vilkas that a phosphatidyl-inosito-dimannoside is the principal component of these phospholipids, and we have proposed for this compound formula (XXVIII), in which inositol is linked to the C-1 or C-3 atom of the *meso*-inositol, and in which the exact position of the 6-*O*-α-D-mannopyranosido-α-D-mannopyranose is not yet known[53]. The fatty acid molecules linked to glycerol are normal and methyl-branched C_{16} to C_{18}-fatty acids.

The phosphatidyl-inosito-dimannoside is accompanied by other phospholipids, amongst which a phosphatidyl-pentamannoside[54, 55] and a phosphatidyl-pentaglucoside[56] are most remarkable.

In the course of recent immunization experiments conducted in collaboration with Bloch, Vilkas obtained fractions of phospholipids which produce (in 20 μg doses) a distinct increase in survival time of mice; the main constituent of these high-melting, strongly dextrorotatory fractions seems to be a phosphatidyl-inosito-trimannoside*.

THE MYCOSIDES, TYPE-SPECIFIC GLYCOLIPIDS

Smith *et al.*[57, 58], using the combined techniques of chromatography and infra-red spectroscopy, were able to show that some lipid compounds are limited in distribution to a single species of micro-organism; their presence or absence may thus serve to distinguish between various species of Mycobacteria.

The distribution of these substances in the various species of Mycobacteria is as follows[58]: (i) phthiocerol dimycocerosate is present in the lipids of 28 out of the 30 human strains studied; (ii) a compound, first called G_B, is present in all 7 bovine strains studied; (iii) a compound, first called G_A, is present in all 17 photochromogenic strains studied; (iv) a compound, called Jav, is present in 11 out of 13 avian strains, and also in 3 out of 6 non-photochromogenic strains.

As it was then shown[59] that compounds G_A, G_B and Jav are glycolipids, containing characteristic *O*-methylated 6-deoxyhexoses in glycosidic linkage, it was suggested that these compounds be called " mycosides "; a mycoside is defined as a " type specific glycolipid of mycobacterial origin "[60].

Mycoside A (the former G_A) is a nearly colourless solid, melting at 105°, $[\alpha]_D = -37°$; it contains three different *O*-methylated 6-deoxyhexoses, which have been identified as 2-*O*-methylfucose, 2-*O*-methylrhamnose and 2,4-di-*O*-methylrhamnose[59]. The lipid moiety of mycoside A is a di- or tri-mycocerosate of an aromatic alcohol with a typical ultra-violet light absorption spectrum (maxima at 222, 274 and 278 mμ in hexane).

Mycoside B (the former G_B) is a colourless wax melting at 25°, $[\alpha]_D = -22°$; it has approximately the same ultra-violet light absorption maxima as mycoside A; the probable molecular formula is $C_{82}H_{152}O_{10}$; mycoside B contains only one sugar, identified by MacLennan *et al.*[59] as 2-*O*-methyl-rhamnose.

The lipid moiety of mycoside B has the formula $C_{75}H_{140}O_6$ and is a diester of two molecules of a branched-chain acid fraction of mean molecular composition $C_{22}H_{44}O_2$, with a methoxylated phenolic triol $C_{31}H_{56}O_4$. In mycoside B, the deoxyhexose is linked glycosidically to the one phenolic hydroxyl-group of the lipid moiety (Demarteau-Ginsburg and Lederer, unpublished experiments).

Mycoside C differs from the other mycosides by its nitrogen content, which is due to the presence of several amino-acids; mycoside C is a peptido-glycolipid; as a matter of fact, it is a mixture of closely-related compounds which can be separated by chromatography on silicic acid; three of the fractions thus obtained have been investigated in more detail (see *Table 2*)[61].

The peptide portion of these three fractions contains three different amino-acids linked in a pentapeptide: one molecule of D-phenylalanine

* More recently, the immunizing activity of this faction has been rather irregular.

Table 2. Composition of three different fractions of mycoside C

		Fraction I/17	*Fraction* II/7	*Fraction* III/7+8
Melting point		~200°	~200°	195–200°
$[\alpha]_D$ *(in chloroform)*		+44°	−34°	−34°
Probable molecular formula		$C_{79}H_{131}N_5O_{23}$	$C_{80}H_{137}N_5O_{24}$	$C_{85}H_{111}N_5O_{23}$
Products of hydrolysis	*Hydroxyacid*	$C_{24}H_{45}O_3 \pm 2CH_2$	$C_{23}H_{44}O_3 \pm 2CH_2$	$C_{20}H_{38}O_3 \pm 2CH_2$
	Acetic acid (moles)	2	2	2
	Deoxyhexoses[a] (moles)	4	3	3
	Amino-acids (moles)	1 D-Phe 2 D-allo-Thr 2 D-Ala	1 D-Phe 2 D-allo-Thr 2-D-Ala	1-D-Phe 2-D-allo-Thr 2-D-Ala

[a] The deoxyhexoses of these fractions have been identified by MacLennan[63]; they are: 6-deoxytalose, 3-*O*-methyl-6-deoxytalose and 3,4-di-*O*-methylrhamnose.

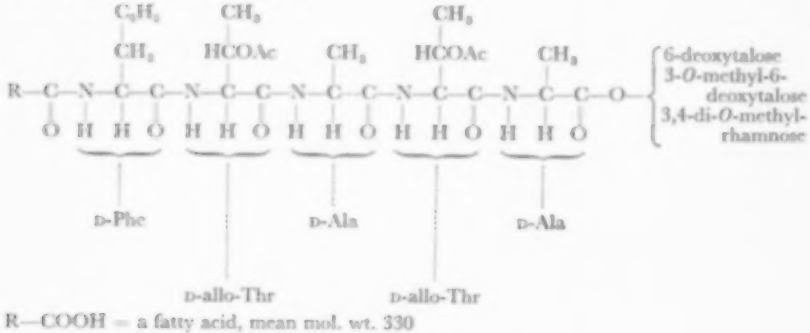
(Phe), two molecules of D-allo-threonine (Thr) and two molecules of D-alanine(Ala); the pentapeptide of fraction III/7 + 8 has the structure:

D-Phe.D-allo-Thr.D-Ala.D-allo-Thr.D-Ala.

The unnatural configuration of all the constituent amino-acids, and the presence of D-allo-threonine (which had not previously been isolated from natural sources), are remarkable features[63].

These mycoside C preparations contain three different 6-deoxyhexoses: 6-deoxytalose, 3-*O*-methyl-6-deoxytalose and 3,4-di-*O*-methylrhamnose (MacLennan[63]). It can be seen from *Table 2* that fraction I/17 contains four molecules of deoxyhexoses, whereas the other two fractions contain three molecules.

The lipid moiety of these mycoside C preparations has not yet been fully characterized; it seems to be a mixture of saturated and unsaturated hydroxyacids, the approximate molecular formula of the saturated acids varying from $C_{20}H_{40}O_3$ to $C_{30}H_{60}O_3$. Two *O*-acetyl groups are also present in each of these fractions. For fraction III/7 + 8, the tentative structure (XXIX) has been proposed:



R—COOH = a fatty acid, mean mol. wt. 330

(XXIX)

VOL. 2 1961

In this structure, the terminal carboxyl group of D-alanine is not free but esterified with a hydroxyl group of one of the sugar molecules. As the three mycoside C fractions studied all have two molecules of D-allo-threonine and two *O*-acetyl groups, it is assumed that the acetyl groups are esterified to the hydroxyl groups of allo-threonine.

Amongst the apparently type-specific lipids, we might also mention a sugar-free peptido-lipid isolated from the pathogenic Actinomycete *Nocardia asteroïdes*[64]; this fraction is a mixture of closely related compounds, m.p. 215–217°; $[\alpha]_D = +44{\cdot}5°$, consisting of 30 per cent of a lipid moiety of approximate molecular formula $C_{22}H_{64}O_2$, joined by an amide linkage to an oligopeptide containing the following six amino-acids: threonine, alanine, valine, isoleucine, leucine and proline. Two-thirds of the alanine and isoleucine are D-; here again the presence of D-amino-acids is noteworthy[62].

CONCLUSION

In the course of a detailed study of the relations between biological activity and chemical structure of bacterial lipids, we have determined the structure, and mechanism of biosynthesis, of high molecular weight branched-chain hydroxyacids. New types of glycolipids and peptido-glycolipids have been isolated, and their chemical structures have been defined; their interesting biological activities have been characterized.

The simultaneous presence of several lipophilic and hydrophilic groups in the same molecule confers to glyco- and peptido-glycolipids peculiar physicochemical properties (such as emulsification, detergent action, *etc.* . . .) which might explain many of their biological activities and which open new fields of investigation.

Whereas D-amino acids had previously been known to exist only in antibiotics and in bacterial cell-walls, the work described above shows that they are also frequent constituents of liposoluble bacterial products, such as peptido- and peptido-glycolipids. This might indicate a close biochemical and physiological relationship of these products with cell-wall.

The work of our group has been greatly facilitated by large supplies of bacteria, due to the kindness of Drs J. Tréfouël and J. Bretey (Institut Pasteur), by several grants from the "Fondation Waksman pour le Développement des Recherches microbiologiques en France" and, more recently, by Grant E 28–38 of the National Institute for Allergy and Infectious Diseases (National Institute of Health, Bethesda, Md., U.S.A.).

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VOL. 2 1961

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VOL
2
1961

THE BIOSYNTHESIS OF POLYISOPRENOIDS

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To a chemist, a natural product may be a structural problem, an objective for synthesis, an exhibitor of chemical and physical properties, or perhaps mere raw material. The tendency to regard it as a sample of the living organism's synthetic power is more recent, and experimental investigation of that power is more recent still. Such experiments depend on the use of isotopic tracers, and they alter the traditional objectives and values in an interesting manner. Thus, before isolation of a natural product, the organism must be induced to make it from an isotopically labelled precursor; chemical degradations are directed not to elucidation of structure but to unambiguous location of labelled atoms; and complicated and novel syntheses may be needed to prepare a specifically-labelled intermediate. And, eventually, the student of biosynthesis may find himself looking on certain large classes of natural products not—as he ought to do—as rich collections of beautiful chemistry, but as conglomerations too variable to be of great importance in the fundamental chemistry of life, where universal occurrence of the same or very similar substances seems to be the rule.

And yet—it was the very existence of large classes of chemically related natural products that stimulated the first speculations on biosynthesis. As Robinson has pointed out[1], these hypotheses, of which his own on alkaloids and Ruzicka's on terpenes are the most notable examples, were based on structural grounds; indications of the exact chemical nature of precursors could not be precise. That, even so, they often came near the truth is a tribute to the chemical intuition of the pioneers, and perhaps also a sign that enzymic processes do come within the scope of an intuition developed by the contemplation of reactions *in vitro*. It is pleasant to record that a structural speculation, made long before it could have been verified, assisted the establishment of squalene as a crucial intermediate in the biosynthesis of many polyisoprenoids; but it is even more satisfactory to note how hypotheses both structural and mechanistic have blended with chemical and biochemical experiment in piecing together the story which I hope now to unfold.

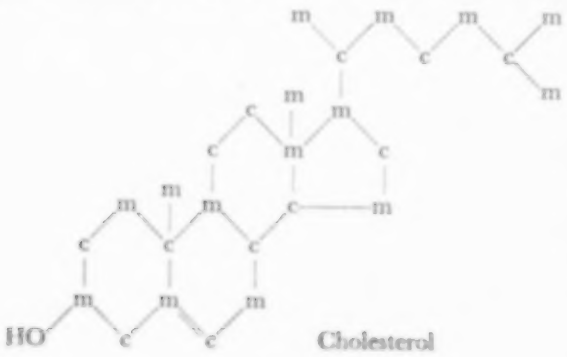
Actual work on the biosynthesis of polyisoprenoids began with the recognition that acetic acid is an important precursor of steroids. Sonderhoff and Thomas[2] found in 1937 that a large excess of deuterium is present in the unsaponifiable fraction—mainly ergosterol—of yeast grown in a medium containing trideuteroacetic acid. This result was extended to animal tissues by Bloch[3], whose studies, at first with Rittenberg and later at the head of his own group, outweigh all other contributions to knowledge of steroid biosynthesis.

When the carbon isotopes, especially ^{14}C, became available as tracers, it was quickly shown that both carbon atoms of acetate were incorporated

into cholesterol, the methyl carbon to a somewhat greater extent. But the prospect of obtaining more detailed information first became apparent when Little and Bloch[4] degraded cholesterol, biosynthesized from isotopic acetate, to fragments representing some individual carbon atoms of the side-chain. Those positions in cholesterol which were labelled when methyl-labelled acetate was the precursor were inactive when carboxyl-labelled acetate was used, and the converse was also true. Moreover, quantitative comparison of the radioactivities of cholesterol and of the fragments indicated that all 27 carbon atoms of cholesterol could originate from acetate; about 15 from methyl and 12 from carboxyl groups.

It was remarkable that from so simple a precursor an obviously complicated biosynthesis occurred without that mixing of labels which confused, for example, studies on biosynthesis of aromatic amino-acids and on the photosynthetic fixation of carbon dioxide. However, the opportunities in animal metabolism for acetate to mix its labels are limited. Methyl-labelled acetate can, indeed, be converted into carboxyl-labelled acetate by becoming involved in the citric acid cycle, and this effect seemed to operate to a small extent in our own preparations of cholesterol. Even so, the pattern of labelling in cholesterol appeared perfectly clear-cut, and the complete elucidation of that pattern a worthwhile object. The experimental method was to prepare two specimens of radioactive cholesterol, one biosynthesized from acetate labelled with ^{14}C in the methyl group, the other from acetate similarly labelled in the carboxyl group. The use of rat-liver slices and later of rat-liver homogenates for the biosynthesis made this stage relatively simple. Then, after suitable dilution, each specimen was degraded so as to obtain, in sufficient amount to measure radioactivity, fragments representing each carbon atom of the molecule. Bloch and his collaborators[5] identified the pattern in the eight side-chain carbons and at C–7 of the nucleus[6], and obtained evidence on the origin of two other nuclear carbons. Popják and I, with Hunter[7] and Youhotsky Gore[8], identified all the nuclear carbons except C–7. Dauben[9] and collaborators independently investigated C–7 and, by their extensive degradations of ergosterol[10] and eburicoic acid[11], went far to establish in these two substances the same pattern that emerged from the studies on cholesterol.

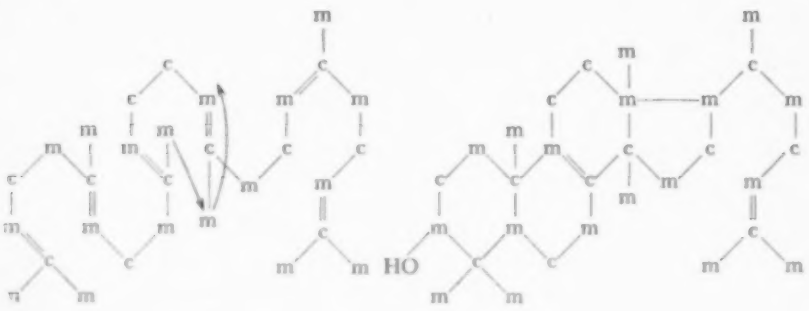
Thus the complete pattern of "methyl" carbons (m) and "carboxyl" carbons (c) in cholesterol biosynthesised from acetate was established:



Cholesterol

But, long before this work was complete, the pattern of labelling in the side-chain had recalled to Bloch a suggestion put forward by Bonner and Arreguin[12] for the biosynthesis of the rubber hydrocarbon from acetate. The idea was wrong, but had enough truth in it to give for rubber a predicted distribution of methyl and carboxyl carbons similar to that found in the side-chain of cholesterol. This hint of a relationship between steroids and terpenes led Bloch to examine the old hypothesis that squalene is a precursor of cholesterol. With the help of ^{14}C, it was not too difficult to prove[13] that squalene was indeed produced from acetate *in vivo*, and that this squalene was further transformed quite efficiently into cholesterol.

Soon afterwards, an important contribution came from Woodward and Bloch[14], who postulated for squalene a mode of cyclization which could lead to the tetracyclic system of the sterols. A particularly interesting feature was that the triterpene alcohol lanosterol could be the first product of cyclization:

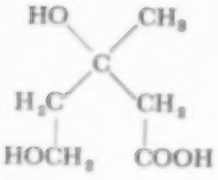


Squalene Lanosterol

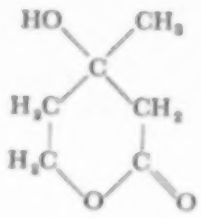
Evidence was produced, and later fully confirmed, that this mode of cyclization was consistent with the actual labelling pattern found in cholesterol biosynthesized from acetate, provided that the acetate units were associated in the expected manner to form squalene. Popják and I were able to show[15], by a total degradation of squalene biosynthesized from methyl-labelled acetate, that the pattern in squalene was in truth the expected one. The complete agreement of the two patterns, given the postulated mode of folding for cyclization, is evident. And, when Clayton and Bloch[16] showed that lanosterol is biosynthesized from acetate and converted into cholesterol *in vivo*, the sterols took what terpene chemists would consider their proper place as degenerate triterpenes.

At this point, the first stage of the investigation could be called complete: there was a clear picture of a biosynthesis proceeding from acetate *via* squalene and lanosterol to cholesterol. It remained to fill in gaps between intermediates, to study the enzymic reactions mediating each stage, and thus to arrive at as complete an understanding of a biosynthetic process as is at present possible.

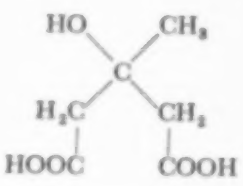
The longest gap lay between acetate and squalene, and attempts to bridge it were not very successful until 1956. A team at the Merck laboratories had been studying a growth factor which could replace acetate in the culture of *Lactobacillus acidophilus*. Folkers and his collaborators finally isolated the factor[17], and identified it as an optically-active 3,5-dihydroxy-3-methylvaleric acid, now known as mevalonic acid. What the *Lactobacilli* need it for is still, I believe, unknown. It is obviously similar in structure



Mevalonic acid



Mevalonic lactone



3-Hydroxy-3-methyl-glutaric acid

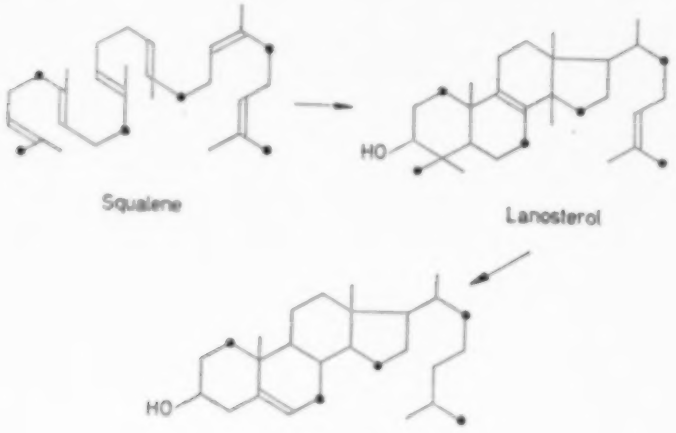
to 3-hydroxy-3-methylglutaric acid, which was known at the time to be built up, with the expected labelling pattern, from acetate in the liver, and to serve as a source of carbon for cholesterol, albeit a poor one, in the rat. Tavormina, Gibbs and Huff[18] were inspired by this structural similarity to prepare racemic mevalonate labelled at C-2 with ^{14}C and to try it as a precursor of cholesterol. In the event, over 40 per cent of the radioactivity of the acid was incorporated into cholesterol by a liver homogenate. Since it is now known that only one enantiomorph of mevalonate is used, and that one-sixth of the radioactivity of this is lost on the way to cholesterol, the yield first reported was, indeed, slightly more than 100 per cent, but the excess would be within experimental error. Soon afterwards, Tavormina and Gibbs[19] showed that radioactivity in the carboxyl group of mevalonate was not incorporated at all into cholesterol, but lost as carbon dioxide during biosynthesis.

To all workers on polyisoprenoid biosynthesis, these discoveries came like an answer to prayer. Here was a substance, obviously related to 3-hydroxy-3-methylglutarate and thence to acetate, which was capable of losing one carbon atom to give a branched C_5 unit. More, the loss of two additional molecules of water could give isoprene itself, the basis of Ruzicka's structural hypothesis on the biogenesis of terpenes.

It was, of course, necessary to be sure that these carbon atoms of mevalonate were being used without prior dissociation. Popják and I, with Mrs Cornforth and Youhotsky Gore, were able to show[20] that 2-^{14}C-mevalonate, when incubated with liver preparations in the absence of oxygen, was largely incorporated into squalene rather than into cholesterol, and a total degradation of the squalene thus synthesized revealed only six labelled positions, the positions predicted for integral incorporation of the C_5 unit into squalene. This is shown in the diagram below, black circles being

VOL. 2 1961

used to indicate the labelled positions in squalene, lanosterol and cholesterol biosynthesized from 2-^{14}C-mevalonate:



Squalene

Lanosterol

Cholesterol

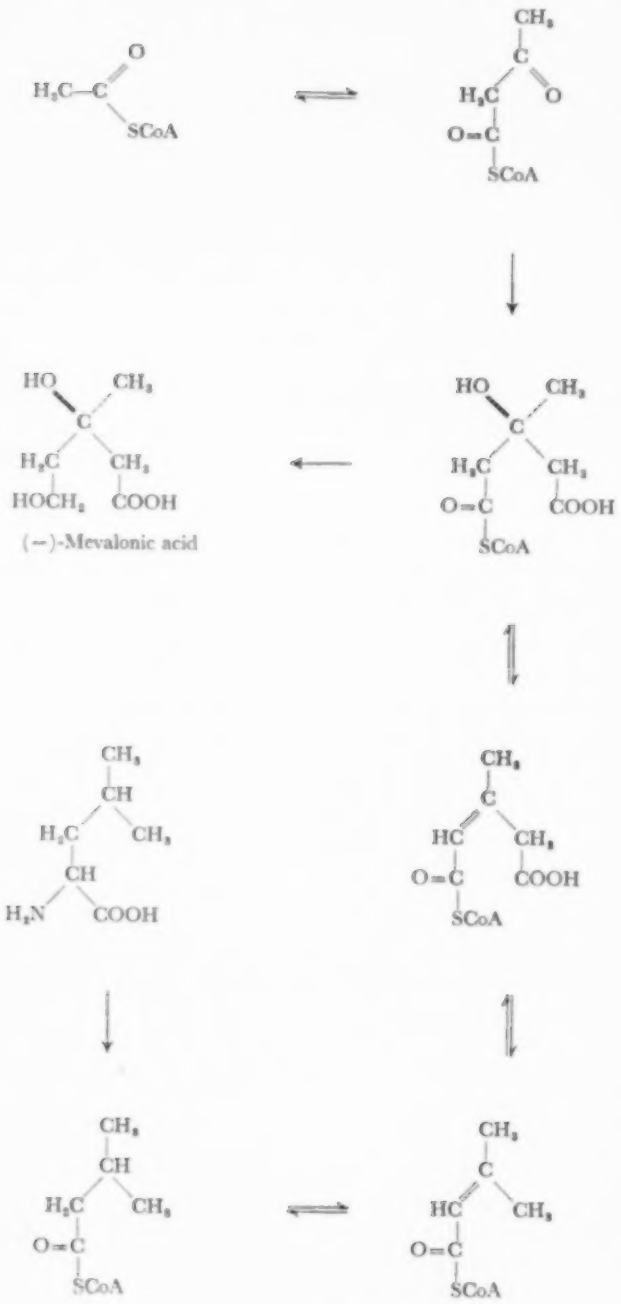
Dituri, Gurin and Rabinowitz[21] independently produced similar evidence, and Isler and this group[22] have done much the same thing for cholesterol biosynthesized from 2-^{14}C-mevalonate; here, measurements of radioactivity indicated five labelled positions of which three were found where expected. The sixth radioactive atom is incorporated into a ring A methyl group of lanosterol and is lost.

With mevalonate as a very conveniently placed landmark on the path of biosynthesis, the mapping of earlier and later stages was made easier, and it became profitable to use fractionated enzyme systems, mainly from liver and yeast, which could carry out only a limited number of stages. It is possible that every intermediate between acetate and lanosterol has now been identified, and many of the enzymes responsible have been extensively purified as well.

The first two stages (see *Scheme I*), conjugation of acetate with coenzyme A and condensation to acetoacetyl-coenzyme A, are not peculiar to polyisoprenoid biosynthesis and are well-known. Both are reversible, and this seems to have defeated attempts[23] to demonstrate incorporation of acetoacetate into cholesterol as a C_4 unit.

The condensing enzyme which, from acetyl- and acetoacetyl-coenzyme A, produces 3-hydroxy-3-methylglutaryl-coenzyme A has been studied and partially purified by Rudney and Ferguson[24]. It is known that the molecule of coenzyme A liberated during condensation is the one present originally as acetyl-coenzyme A. Also, it is known that the product must have the absolute configuration shown, for Rudney demonstrated that only one-half of a synthetic preparation, but all of an enzymically produced specimen, could act as substrate for reduction to mevalonate. The condensation is not readily reversible, though there is another enzyme[25] which breaks down the product to free acetoacetate and acetyl-coenzyme A.

Scheme 1. Biosynthesis of mevalonic acid



VOL. 2 1961

3-Hydroxy-3-methylglutaryl-coenzyme A seems also to be involved in the metabolism of the amino-acid leucine (see *Scheme 1*). Oxidative breakdown of leucine can give isovaleryl-coenzyme A and thence 3-methylcrotonyl-coenzyme A. From work by Coon[26] and Lynen[27] it is known that this can be carboxylated enzymically, and that the glutaconic ester so formed can be hydrated by an enoyl hydrase (methylglutaconase) to hydroxymethyl-glutaryl-coenzyme A. Thus breakdown of leucine can be associated with biosynthesis of steroids and terpenoids, though to what extent this actually occurs is uncertain.

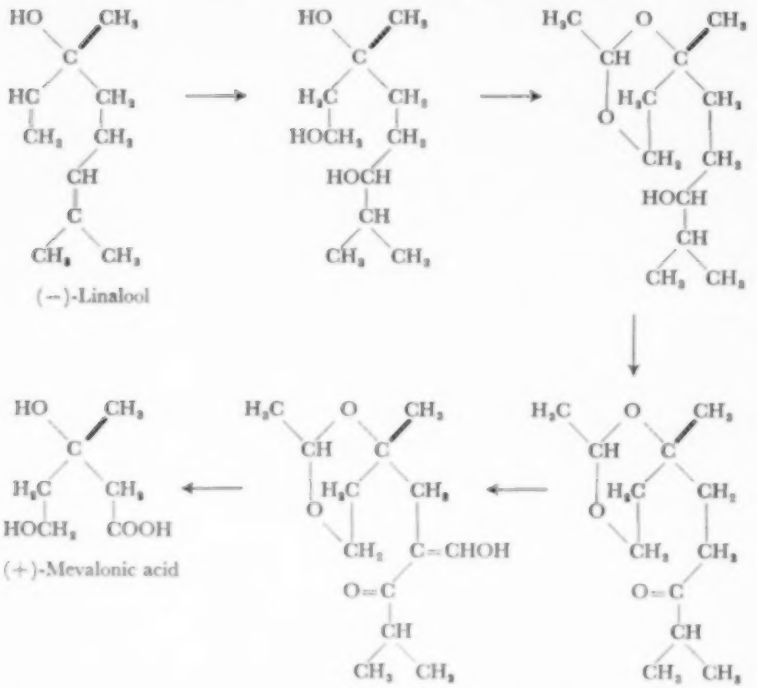
The next enzymic step produces mevalonic acid directly (see *Scheme 1*). The immediate reducing agent seems to be triphosphopyridine-nucleotide, the group operated on is the thiol ester, coenzyme A is liberated (never to participate again in the biosynthesis), and the process seems to be practically irreversible. One might expect a reaction of this sort to proceed *via* an aldehyde as intermediate, but attempts to trap this aldehyde, mevaldic acid, have been uniformly unsuccessful. The enzyme has been studied by the groups of Lynen[28] and Rudney[29]; its mechanism should be interesting to study, for irreversibility in a process of this kind is not usual; and further, the biosynthesis of polyisoprenoids in the tissues so far studied seems to be cut off at this point from other metabolic processes and to proceed almost undisturbed to its goal.

The chemistry of mevalonic acid, and of its lactone which is easily formed and hydrolysed, has been extensively studied; and six or seven syntheses have been devised, one or other of which would permit almost any type of labelling. Natural mevalonate, the growth factor for *Lactobacilli*, is optically active and gives a benzhydrylamide which is laevorotatory in ethanol. We have shown that, when racemic 2-^{14}C-mevalonate is fed to rats[30], approximately half the radioactivity is excreted in the urine, and that this is recoverable as a dextrorotatory mevalonyl-benzhydrylamide. Nearly all the retained radioactivity is found in cholesterol. Thus the enantiomorph which is the growth factor for *Lactobacilli* is also the precursor of steroids.

The absolute configuration of mevalonic acid has been deduced by Arigoni[31] by a chemical correlation with quinic acid, which had itself been correlated with D-glucose. Mrs Cornforth and I were recently able to make a further correlation by means of a synthesis (see *Scheme 2*) which was designed to obtain optically active mevalonic acid in quantity, resolution of the racemic acid being particularly difficult. We started from (−)-linalool which is commercially available. A Brown reaction of this with boron hydride in tetrahydrofuran was followed by oxidation with alkaline hydrogen peroxide, when the expected triol was formed in high yield. Two of the hydroxyl groups were " tied up " by reaction with acetaldehyde, and the third was then oxidized by chromic acid in pyridine to a ketone. This was formylated with methyl formate and sodium methoxide. The crude hydroxymethylene-ketone was smoothly converted with sodium periodate into mevalonic acid, isolated as the crystalline lactone.

We had expected, on the basis of the absolute configuration assigned to linalool by Prelog and Watanabe[32] in 1957, to obtain " natural " mevalonic acid from this synthesis, and it was an unpleasant surprise to find that the benzhydrylamide was dextrorotatory and the acid enzymically inert. The

Scheme 2. Synthesis of mevalonic acid from linalool

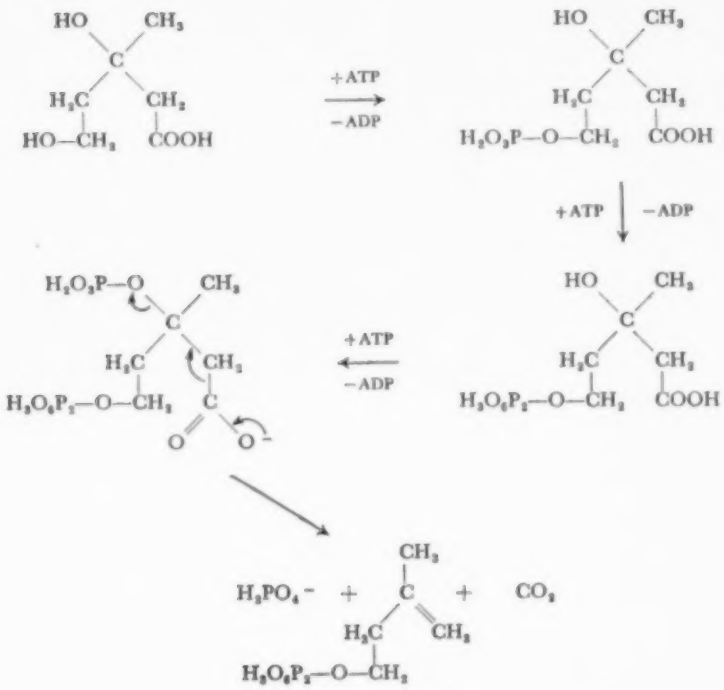


" unnatural " isomer had in fact been formed. Examination of the evidence showed that the assignment of configuration to (−)-linalool, which was founded on an asymmetric synthesis of tetrahydro-linalool, contained an error of interpretation, and that the configurations assigned to the two optical isomers must now be reversed[33]. It was satisfactory that the method of asymmetric synthesis then gave yet another result in agreement with that of direct chemical correlation; but we were not pleased, for (+)-linalool is hard to come by.

It has been found convenient by Bloch and by Lynen to study the stages between mevalonate and squalene in enzyme systems prepared from yeast, and Popják has now overcome the difficulties of demonstrating that the same processes also occur in liver. The first step is a phosphorylation of the primary alcoholic group in mevalonate (see *Scheme 3*). The " natural " enantiomorph is the only one attacked; the enzyme, called mevalonic kinase, has been extensively purified from yeast by Tchen[34] and from liver by Levy and Popják[35]. Adenosine triphosphate is the phosphorylating agent, and the product can readily be isolated. It is sometimes convenient to use biosynthetic 5-phosphomevalonate instead of racemic mevalonate in enzymic reactions where the presence of " unnatural " mevalonate would be a complication. To separate and identify the hydrophilic substances encountered in this region of the biosynthesis, paper chromatography and paper ionophoresis have been used extensively, and information on the

VOL. 2 1961

Scheme 3. Enzymic conversion of mevalonate to iso-pentenyl pyrophosphate



Isopentenyl pyrophosphate

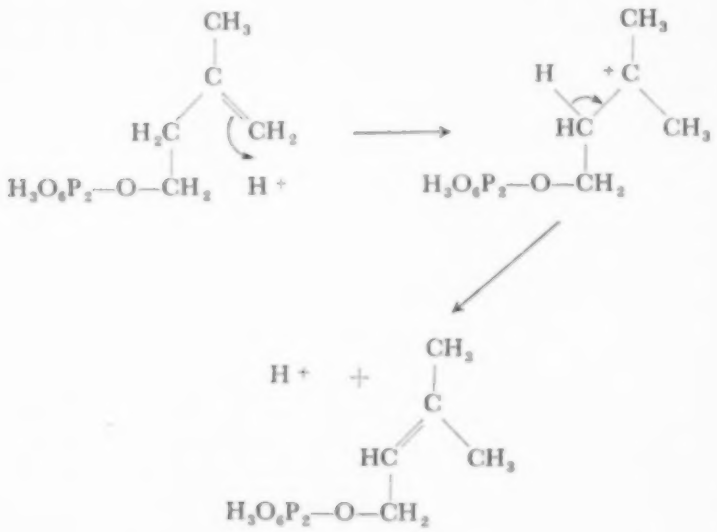
nature of intermediates was also gained by using ^{32}P in conjunction with ^{14}C. Thus, it was shown[36, 37] that the first phosphorylation is immediately followed by another, to give a pyrophosphoric ester. 5-Phosphomevalonate has so far been synthesized only as a racemate. Enzymically formed 5-phosphomevalonate is laevorotatory, $[\alpha]_D = -6{\cdot}1°$.

It is in the next stage that the superfluous carboxyl group of mevalonate is lost. The process can be formulated as a dehydration–decarboxylation of a not unfamiliar type; however, adenosine triphosphate is a necessary cofactor, and it was shown[38], by using isotopic phosphorus in its terminal phosphate group, that this group is set free as orthophosphate during this reaction. Bloch[39] has recently prepared diphosphomevalonate labelled at the tertiary hydroxyl group with ^{18}O, and has shown that the isotope appears in this inorganic phosphate. The presumption is that ATP first phosphorylates the tertiary hydroxyl group, and that a concerted elimination of orthophosphate and carbon dioxide then occurs. That the process is concerted and not an elimination followed by a decarboxylation seems to follow[38] from experiments indicating that tritium is not incorporated from the medium during the enzymic reaction.

The product of this elimination is isopentenyl pyrophosphate, an intermediate discovered and synthesized by Bloch's and Lynen's groups[36, 40, 41].

It will be noticed that this substance is isoprene + pyrophosphoric acid, and it can, in fact, be regarded as the actual chemical basis of Ruzicka's isoprene rule. Its conversion into squalene and cholesterol by suitable enzyme preparations without ATP has been demonstrated. With the newer methods of phosphorylation now available to make its synthesis more convenient, it may well become the precursor of choice for experiments on terpenoid and carotenoid biosynthesis in plants.

Isopentenyl pyrophosphate has a terminal isopropenyl group, whereas squalene, rubber, and many acyclic polyterpenoids have terminal isopropylidene groups. It was, therefore, reasonable for Lynen[42] and colleagues to postulate a prototropic change to dimethylallyl pyrophosphate as a preliminary to the association of C_5 units, and he was able to find in yeast an enzyme able to effect this change reversibly with artificially introduced radioactive substrate:



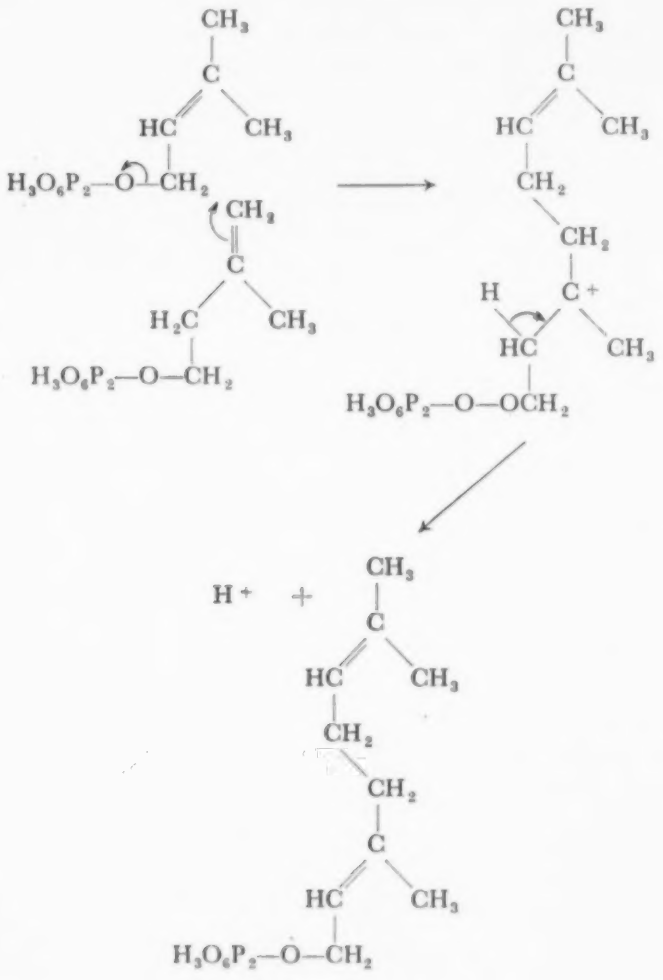
Dimethylallyl pyrophosphate

That the change was an essential one for biosynthesis of squalene could also be demonstrated[43], for the enzyme happened to depend for activity on a sulphydryl group which could be blocked by iodoacetamide. An enzyme preparation so treated could not synthesize squalene from isopentenyl pyrophosphate alone, but could do so when dimethylallyl pyrophosphate was also added. Thus it was shown not only that isopentenyl pyrophosphate is isomerized to dimethylallyl pyrophosphate, but that isopentenyl pyrophosphate is required again at a later stage.

Clearly, the movement of the double bond to form an allyl pyrophosphate would facilitate the separation of pyrophosphate ion either by ionization or by nucleophilic attack—for example, attack by the available electrons

VOL. 2 1961

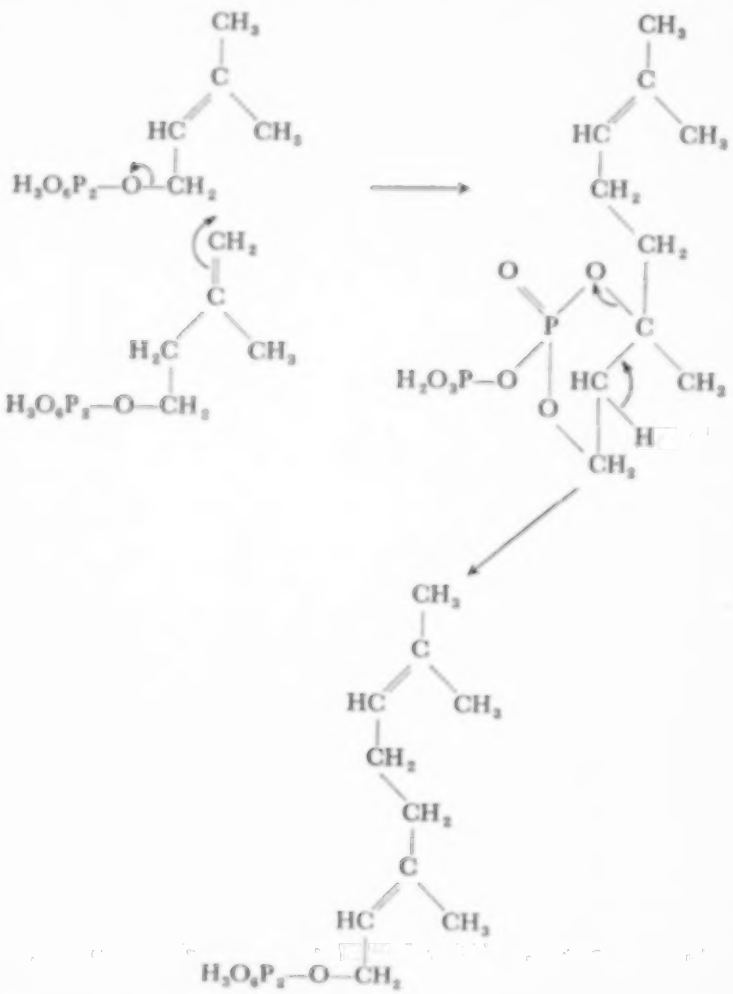
from the double bond of isopentenyl pyrophosphate. The product, which could also, of course, be formed from the olefin and a dimethylallyl cation, might then lose a proton to give geranyl pyrophosphate:



Geranyl pyrophosphate

and Lynen[43] has recently obtained evidence that this substance, which he has synthesized, is indeed formed as an intermediate by his yeast enzyme system. Condensation of geranyl pyrophosphate with a third C_5 unit would then lead to farnesyl pyrophosphate. This also was identified as an intermediate by Lynen[40], and it was recently synthesized by Cramer[44] using a modification of his excellent trichloroacetonitrile method.

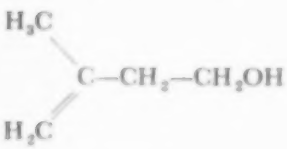
The precise mechanism by which C_5 units are associated is still open to discussion. Johnson[45] recently put forward the interesting suggestion that the pyrophosphate group on the isopentenyl pyrophosphate also facilitates the reaction by an effect of the same kind as is observed, for instance, in the formation of bromo-lactones from bromine and some unsaturated acids. According to this idea, a cyclic phosphate is a stabilized intermediate, and is later cleaved to generate the double bond in a new position. The postulated mechanism may be represented thus:



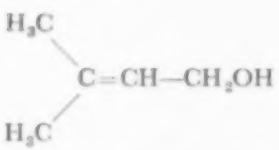
In fact, a solvolysis of benzhydryl chloride in the presence of a suitable unsaturated acid was shown to give carbon–carbon bond formation with concurrent lactonization.

Attractive though it is, the idea does seem to overlook the relatively slight tendency of phosphate ions towards nucleophilic attack on carbon. Perhaps the negatively-charged pyrophosphate residue may rather act electrostatically to polarize the double bond and at the same time to assist removal of the allylic hydrogen. This appears stereochemically possible.

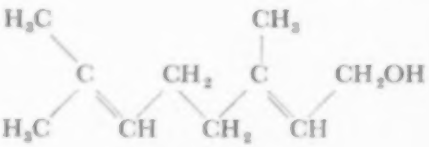
In geranyl pyrophosphate, in farnesyl pyrophosphate and in squalene, there are double bonds capable of geometric isomerism. Natural squalene as the clathrate in thiourea is undoubtedly the all-*trans*-form, as first shown by the X-ray crystallographic data of Nicolaides and Laves[46]. Since natural geranyl pyrophosphate and farnesyl pyrophosphate are precursors of squalene, the presumption is that they also are *trans*-, and this is supported by the available evidence. Synthetic metabolically, active geranyl pyrophosphate was made from natural geraniol, which Jackman and Weedon[47] have conclusively proved to be *trans*-, by methods which would not be expected to alter the geometry of the double bond. As for natural farnesyl pyrophosphate, the evidence that this is exclusively in the *trans*,*trans*-form is also strong. Popják has obtained a soluble enzyme system from rat liver which will convert radioactive 5-phosphomevalonate to a range of isoprenoid pyrophosphates. The free alcohols can be liberated enzymically by various phosphatases and examined by gas–liquid radiochromatography[48], a method which permits automatic recording of the retention time, height and total radioactivity of each peak as it emerges from a column of high resolving power. In this way isopentenol, 3,3-dimethylallyl alcohol, geraniol and farnesol were detected:



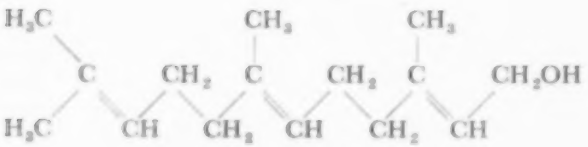
Isopentenol



3,3-Dimethylallyl alcohol



Geraniol



Farnesol

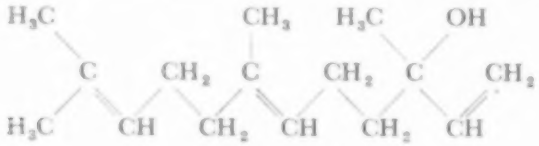
as well as a radioactive peak corresponding in retention time to the C_{20} compound geranylgeraniol. Both geraniol and farnesol appeared as single

peaks, though the column was easily able to resolve geometrical isomers of these alcohols. Geraniol was present as the slower-moving *trans*-isomer and the farnesol peak corresponded to the slower-moving peak of a synthetic product consisting of *cis,trans*- and *trans,trans*-farnesol[49].

The principle of construction of polyisoprenoid chains revealed in all these studies is presumably applicable to the biosynthesis of such natural products as the carotenoids, though evidence on the point is still confined to the demonstration of mevalonate as a precursor. And it is also significant that, with substances such as the ubiquinones and vitamins K_2, the polyisoprenoid chain is attached to an aromatic nucleus by the " tail " carbon. If supplied as an allyl pyrophosphate, this carbon, of course, would be open to nucleophilic substitution of the same type as in the chain-extending process. In long-chain alcohols such as solanesol, in rubber and in gutta-percha, we presumably have examples of the continued operation of this extension. It is true that in rubber the double bonds are *cis*-, but the stereochemical outcome of the synthesis is determined by the spatial orientation of each new C_5 unit added.

The exact nature of the process by which two C_{15} units are united to give the C_{30} compound squalene is not yet determined, and has been the subject of some recent work by Goodman and Popják with Mrs Cornforth and myself. Farnesyl pyrophosphate is undoubtedly a precursor of squalene, conversions having been attained by Lynen with a particulate preparation of yeast, and in especially high yield by Popják with a preparation of rat liver microsomes. The process is a reduction, two electrons being required for synthesis of each molecule of squalene, and for this a reduced pyridine nucleotide, preferably TPNH, is required.

A possible clue to the mechanism was found by Goodman and Popják[49]. When farnesyl pyrophosphate is hydrolysed by acid—this happens very easily—the major product is not farnesol but the tertiary alcohol nerolidol:



Nerolidol

accompanied by both *cis,trans*- and *trans,trans*-farnesol. This observation is easily understood as an allylic rearrangement, but nerolidol also appears, though in much smaller proportion, when the natural pyrophosphates are hydrolysed enzymically at neutral or alkaline pH; nerolidol was also found after fission of the phosphate ester by lithium aluminium hydride. The possibility thus raised, that farnesyl pyrophosphate is naturally accompanied by nerolidyl pyrophosphate, conceivably produced from it by rearrangement, led us to put forward[50] a hypothesis that the coupling of C_{15} units is simply another alkylation of a terminal double bond, here that of nerolidyl pyrophosphate, by an allyl pyrophosphate, here farnesyl. Loss of a proton from the resulting cation would lead to a C_{30} pyrophosphate still of allylic type, which could be expected to lose pyrophosphoric acid with ease to

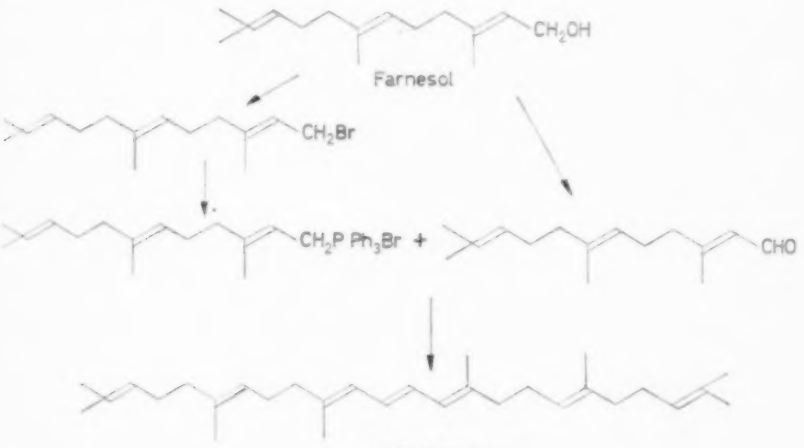
VOL 2 1961

give a conjugated triene, dehydrosqualene, which might then be reduced. The postulated reaction is as shown in *Scheme 4* pp. 622-3.

In putting forward this mechanism, we were influenced by some work by Rilling and Bloch[51] on the uptake and exchange of hydrogen during biosynthesis of squalene from mevalonate. This work may be summarized thus: first, that squalene, biosynthesized from mevalonate in which both hydrogens on C–5 have been replaced by deuterium, contains not twelve deuterium atoms but only about ten; and when this squalene is degraded by ozonolysis, the succinic acid from the four central carbon atoms contains not four deuterium atoms, but only about two. Secondly, squalene biosynthesized from ordinary mevalonate in a deuterium oxide medium contains 3·5 to 4 deuterium atoms, and in a parallel experiment in tritiated water half the tritium introduced into squalene was found in the succinic acid, the other half being furnished by the two hydrogens which are necessarily taken up in forming the terminal isopropylidene groups.

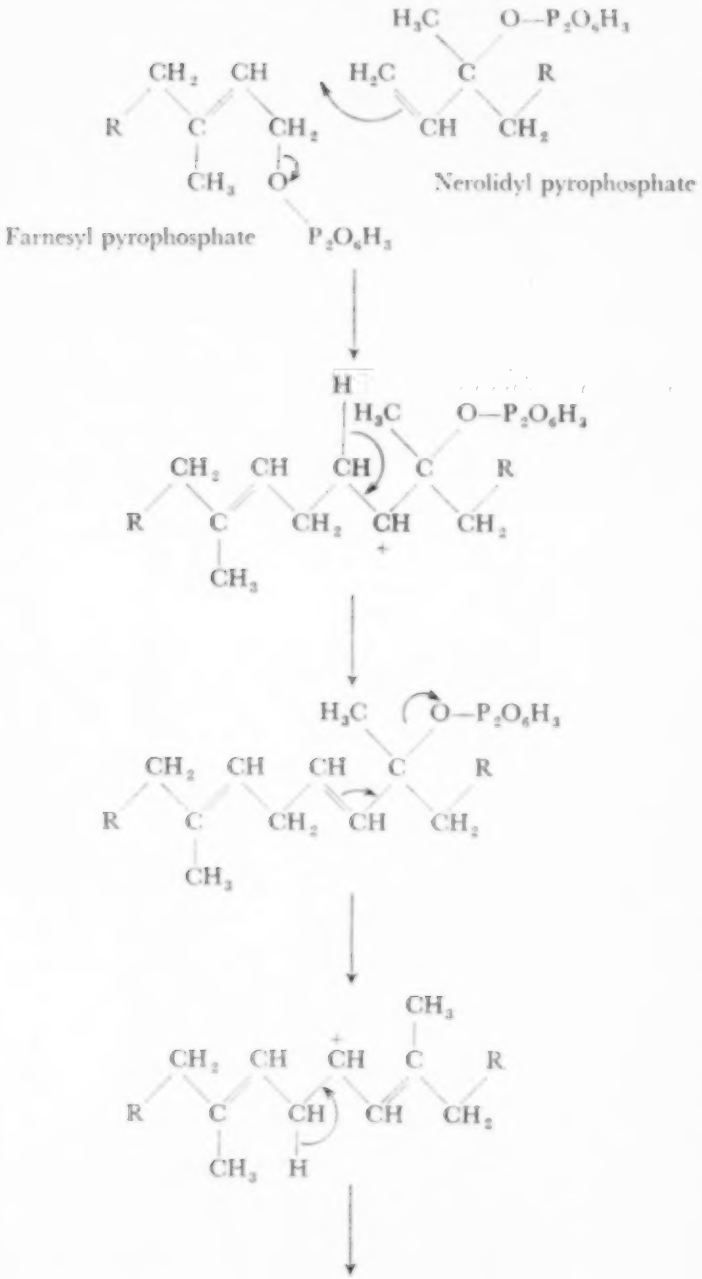
All this seemed clear evidence that two hydrogen atoms, both originally attached to the oxygenated carbon of farnesyl pyrophosphate, are replaced by other hydrogen atoms during biosynthesis of each molecule of squalene; if dehydrosqualene were an intermediate such a replacement would, of course, be inevitable.

We therefore devised some experiments to examine the detailed mechanism of squalene biosynthesis. A chemical synthesis of dehydrosqualene was one objective, and Mrs Cornforth achieved this quite simply. In the first step, farnesol was converted into farnesyl bromide by Rydon and Landauer's[52] method with triphenyl phosphite benzylobromide. The undistilled bromide was immediately treated with triphenylphosphine, when there was formed a phosphonium salt which with farnesal and sodium ethoxide gave dehydrosqualene by a Wittig synthesis. The reaction scheme is illustrated as follows:

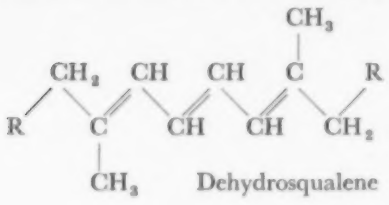


The ultra-violet absorption spectrum of this substance corresponded closely with that of an analogously constituted natural product, the C_{40} compound

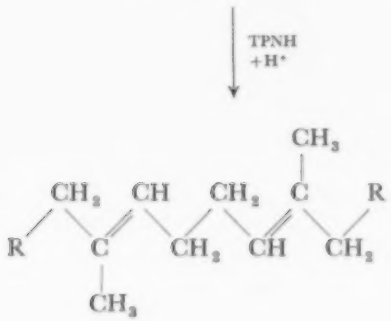
Scheme 4. Postulated biosynthesis of squalene

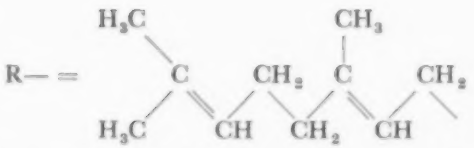


VOL. 2 1961



Dehydrosqualene



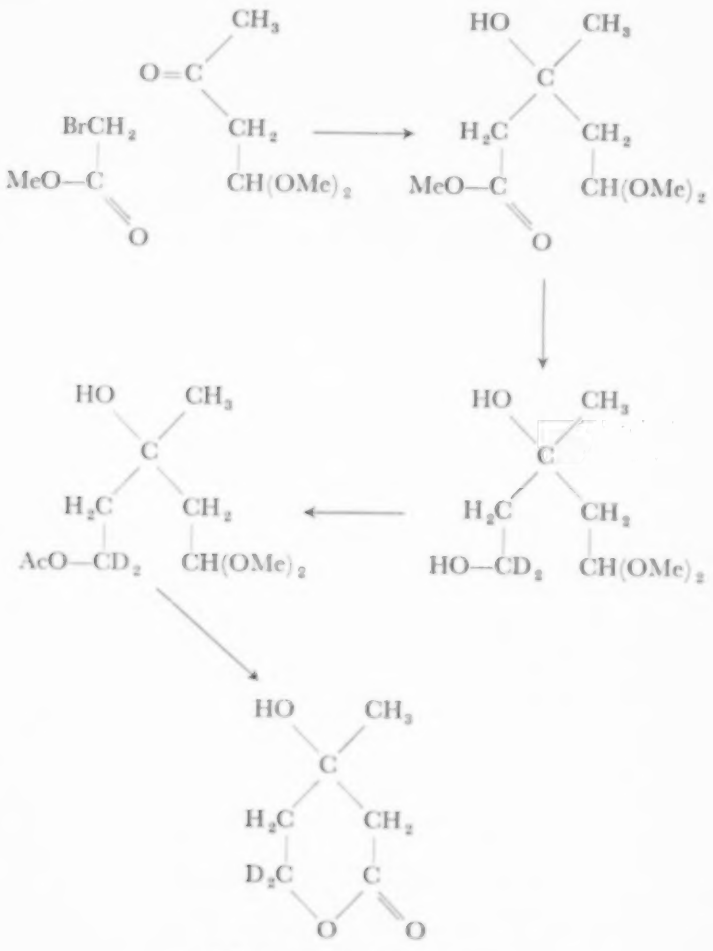


phytoene. The synthetic product was a mixture of geometrical isomers. Preparation of a radioactive dehydrosqualene has not yet been completed, for reasons which will become apparent.

We also wished to check the findings of Rilling and Bloch and to determine, if these findings were confirmed, whether replacement of two hydrogens occurred at one carbon atom or two: in other words, whether the central methylene groups in squalene biosynthesized from 5-D_2-mevalonate (or from normal mevalonate in deuterium oxide) were —CHD—CHD— or —CD_2—CH_2—. To do this, the degradation of squalene would have to be done without the usual dilution with unlabelled carrier.

Two dideuterosuccinic acids were prepared, the symmetrical isomer by adding sodium amalgam to a solution of maleic anhydride in deuterium oxide, the unsymmetrical by heating ethane tricarboxylic ester with deuterium oxide at 150°. Succinic anhydrides prepared from these acids gave excellently resolved infra-red absorption spectra in potassium chloride micro-plates. The two spectra were completely different, and it was demonstrated that 120 micro-grams of either anhydride mixed with three times its weight of unlabelled anhydride could be identified with certainty. In the event, this method did not have to be used, but it showed that deuterated succinic acids suffer little exchange of deuterium on conversion to anhydrides. Later, tetradeuterosuccinic acid was made by heating deuterium oxide with ethane tetracarboxylic ester.

The dideuteromevalonate was prepared by adapting an earlier synthesis of ours. 4,4-Dimethoxybutan-2-one with methyl bromoacetate and zinc gave an acetal-ester which was reduced by lithium aluminium deuteride ("98 per cent D"). The product with hydrogen peroxide in acetic acid containing a trace of sulphuric acid gave crystalline mevalonic acid lactone containing 1·96 atoms of D per molecule, as determined by combustion of a diluted specimen of benzhydrylamide. The reaction scheme is given as follows:



DL-5-D_2-Mevalonic acid lactone

This mevalonate was mixed with a little 2-^{14}C-mevalonate before biosynthesis; the radioactivity was needed to measure the amount of squalene biosynthesized *de novo* in the enzyme system, and also for a check on the origin of the succinic acid obtained from the squalene by oxidation. Squalene

VOL. 2 1961

was also made from non-deuterated ^{14}C-farnesyl pyrophosphate in (i) a deuterium oxide medium, and (ii) a tritiated water medium. Another specimen of squalene was made from non-isotopic mevalonate in normal water with tritiated TPNH.

The biosynthetic squalene was purified by repeated separation as the clathrate in thiourea. A portion was burned after suitable dilution with non-isotopic squalene; the remainder was ozonized without dilution by adding it to excess of ozone in ethyl chloride at — 80°. The ozonide was decomposed with hydrogen peroxide and acetic acid, and, after destruction of excess peroxide, the acids were extracted into ether and the succinic acid crystallized by adding a little chloroform to the evaporated extract. Since 10–20 mg of squalene was available for ozonolysis, the amount of succinic acid did not exceed 1–2 mg, and this had to be recrystallized before conversion into succinic anhydride. A technique was therefore devised which may be of general interest.

The succinic acid in ether was allowed to flow slowly from a fine capillary into a melting-point tube tapered at the bottom and held in a bath at 50–60° (see *Figure 1*). When the transfer of succinic acid was complete, a

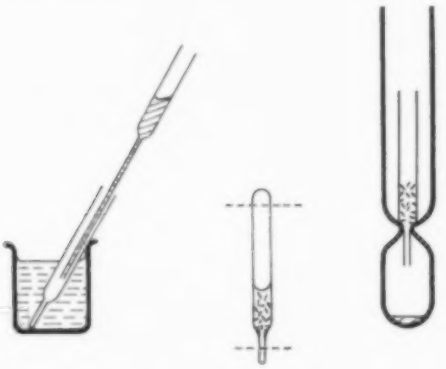


Figure 1. Micro-manipulations of succinic acid

capillary containing 2 μl of water per mg of succinic acid was rested at the top of the tube. Brief spinning in a centrifuge forced the water into the melting-point tube, which was sealed, heated in boiling water until the solid dissolved, spun whilst still hot to collect any sediment at the extreme tip, then cooled and allowed to crystallize. The tube was opened at the top and broken off near the tip. It was then rested on a constriction made in a larger tube, and spun. The crystals could not follow the mother liquor through the narrow orifice and they were washed *in situ* with about 2 μl of ice-water (temperature control of this assembly is not difficult to arrange). After being dried, the crystals were loosened with a fine gold wire and tapped into a new tube, where they were weighed. About twice their weight of acetyl chloride was spun down on them; the tube was sealed and heated for about 2 minutes in a paraffin bath at 90°; reaction was then complete. The liquid was spun into the tapered

end and allowed to crystallize, the mother liquor was removed as above and the succinic anhydride crystals were washed with cold ether. One crystal was then reserved for melting-point determination. Some manipulative losses due to inexperience were encountered, and in our best experiment 470 μgm of succinic anhydride were obtained from 1·43 mg of crude succinic acid.

The samples of succinic anhydride from squalene, and also from the three synthetic deuterated succinic acids, were examined in a high-resolution mass spectrometer, at the Karolinska Institutet in Stockholm, by Dr Ryhage. We are most grateful to him and to Professor Bergstrom who arranged for this examination.

The molecular peaks of succinic anhydride in this spectrometer were small, but the cracking pattern provided the necessary information. The principal mode of fission is to carbon dioxide and a fragment of mass 56 (see *Table 1*). In normal succinic anhydride, the peaks at masses 57–60 are

Table 1. Mass spectra of succinic anhydrides at m/e 56–60. For each sample, the highest peak in the group is given the arbitrary value 100 and values for the other peaks are calculated on this basis

Sample of succinic anhydride	m/e				
	56	57	58	59	60
1. From normal succinic acid	100·0	4·72	0·34	0·28	0·20
2. From normal squalene ozonide decomposed in 1-D-acetic acid	100·0	4·4	0·37	0·07	0·13
3. From 2-D_1-succinic acid (synthetic)	3·78	15·0	100·0	18·9	1·71
4. From 2,3-D_2-succinic acid (synthetic)	4·83	24·0	100·0	4·24	0·5
5. From 2,3-D_2-succinic acid (synthetic)	1·25	2·29	5·48	23·0	100·0
6. From mixture of 1 and 5	100·0	7·18	4·11	14·08	53·3
7. From squalene biosynthesized from 5-D_2-mevalonate	10·5	9·60	46·2	100·0	3·91

small relative to 56, but it is otherwise in the specimen from squalene prepared from deuteromevalonate. Mass 59, a trideuterated species, is seen to predominate, and the proportion of mass 60, which would contain the tetradeuterated species, is scarcely larger than would be provided by the normal content of ^{13}C in the trideuterated fragment. The same thing could be seen in the other major mode of fission, to carbon dioxide, carbon monoxide and ethylene. Mass spectra of the three synthetic deuterated succinic anhydrides are shown in *Table 1* for comparison.

The proportion of succinic acid originating from other parts of the squalene molecule could be measured from the radioactivity of the sample, and was shown to be about 20 per cent of the total. Some, but not all, of the dideuterated species is thus accounted for. We examined the possibility of exchange of deuterium for hydrogen during ozonolysis, but unlabelled squalene ozonide, when decomposed by hydrogen peroxide in deuterated or tritiated water, gave succinic acid having no significant isotopic excess. Succinic acid recovered (with some dilution) from the mother-liquors of the original experiment, also showed the trideuterated species to be predominant when assayed as dimethyl succinate by mass spectrometry.

VOL. 2 1961

These results are entirely incompatible with the hypothesis that the central carbon atoms of squalene biosynthesized from mevalonate carry only two hydrogen atoms originating from mevalonate, since most molecules clearly contain three. Comparison of the total deuterium content of our squalene with that of the mevalonate from which it was made indicated that each squalene molecule contained eleven of the twelve deuterium atoms in the six molecules of precursor (see *Table 2*). Like the mass spectrometry, this indicates exchange of one hydrogen atom, but the origin of the

Table 2. Deuterium content of squalene biosynthesized from 5-D_2-mevalonate

	Atoms per cent excess of D
Found	0·266
Corrected for dilution	20·9
Calculated for 11 hydrogen (+ deuterium) atoms originating from C-5 of mevalonate (95·1 atoms per cent excess of D)	20·9
Calculated for 10 atoms	19·0
Calculated for 12 atoms	22·8

new hydrogen remains obscure, for squalene biosynthesized from farnesyl pyrophosphate by the squalene synthetase system in deuterium oxide gave succinic anhydride showing no excess whatever of deuterated species; and the incubation of normal mevalonate with the enzyme system and tritiated TPNH gave squalene containing very little tritium.

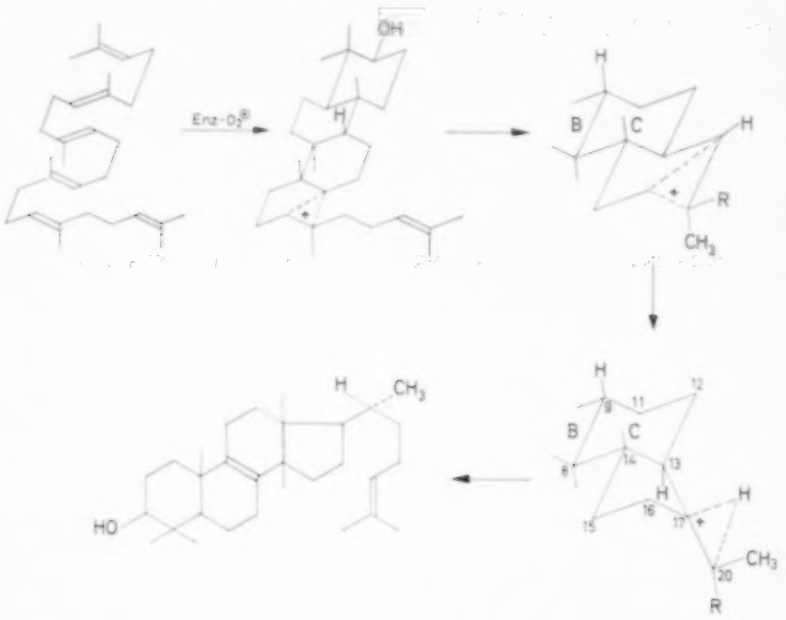
We cannot explain the discrepancy between these results and those of Rilling and Bloch*. However, our hypothesis of the biosynthesis of squalene by way of dehydrosqualene is proved incorrect and must be withdrawn. And, if the data indicating exchange of one hydrogen atom during biosynthesis are accepted, no mechanism yet proposed (*e.g.* by Lynen *et al.*[40]) is consistent with the facts. It would seem that the coupling of C_{15} units is a more complex process than had been thought.

Finally, we come to the cyclization of squalene; and here, in contrast, chemical prediction has constantly anticipated the results of biochemical experiment. In 1955, not long after squalene was established as a precursor of cholesterol, Ruzicka and his colleagues published a paper[53] which might be termed the apotheosis of the isoprene rule. Essentially, the cyclizations of squalene were pictured as reactions of an electron-deficient centre with the available electrons of a double bond. In chemistry of this sort, 1,2-shifts of hydrogen and alkyl groups are common. Some well-grounded assumptions were made about the stereochemistry of these additions and rearrangements. Detailed mechanisms for the biosynthesis from squalene of all known types of triterpenes could then be formulated, while observing the added condition of non-stop reaction: that is, the initiating electron-deficiency was not lost at any intermediate stage.

This theory, as applied to the biosynthesis of lanosterol, postulates an initiating species equivalent to a hydroxyl cation. A concerted cyclization

* This anomaly has since been resolved (G. Popják, De W. S. Goodman, J. W. Cornforth, R. H. Cornforth and R. Ryhage. *Biochem. Biophys. Research Commun.*, **4**, 138 (1961). The source of the "new" hydrogen atom is shown to be TPNH.

then leads to an intermediate in which the electron-deficiency has been transferred to what will be C–20. A rearrangement occurs, the effect of which is to invert the configuration of the carbonium ion. A series of four 1,2-shifts is then possible, two hydrogen atoms and two methyl groups migrating; and finally the positive charge is lost as a proton from C–9, leaving lanosterol. This cyclization of squalene to lanosterol is represented (after Eschenmoser *et al.*[53]) as follows:



All experimental facts so far available are consistent with this view. In particular, Bloch's group[54] and our own[55] have examined the rearrangements of the two methyl groups. This was a difficult problem, because the symmetry of squalene made it impossible to label only one of the groups, and both solutions were based on the fact that a mass spectrometer can distinguish molecules containing one isotopic atom from those containing two. We were able to show that the C–18 methyl group of cholesterol had arrived there by intramolecular migration from C–14, and our Harvard colleagues showed that the methyl group on C–14 of lanosterol is not the group occupying a corresponding position in squalene but has also arrived there by migration. All this is in strict accord with theory.

Theoretically, the position of squalene as the mother of triterpenes seems unassailable, but lanosterol is still the only triterpene of which squalene is actually proved to be the precursor. Arigoni's demonstration[56] that soyasapogenol B is biosynthesized from acetate and from mevalonate seemed also to show that the labels in both these precursors had become somewhat mixed. No doubt the tracing of a biosynthetic pathway in a higher plant will raise difficulties, and will require more workers in this field than are

VOL. 2 1961

yet available. Perhaps I may end on this note, for if even one of those present should be moved to experiment by the story I have tried to tell, then your patience in hearing it might be rewarded.

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VOL.
2
1961

SUMMARY OF SCIENTIFIC ACHIEVEMENTS OF THE SYMPOSIUM

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It would be presumptuous for me, or anyone else for that matter, to pretend to be able to perform adequately the task which I must now attempt. For one thing, none of us has been able, as we might have wished, to be in three places at the same time. Furthermore, the preprinted abstracts are largely of the nature of appetizers, an invitation to the lunch; but with a masterly reticence in regard to the menu—to say nothing of the details of the cooking. Nevertheless, there is much more to be said than I can possibly cram into half-an-hour, and I can only plead for merciful consideration of the extenuating circumstances and recognition of the fact that my remarks will inevitably be coloured by personal scientific interests and by my own predilections and, perhaps, prejudices. It is in that light you should view my estimate of the Symposium as a whole. For me, it has been an entrancement throughout, a spectacular demonstration of rapid progress and vitality, and a pledge for future advances. I am not here to make dogmatic comparisons of merit or significance. The highlights which I shall mention may appear dazzling to me, because I am relatively near to them; more remote stars in the galaxy may, of course, be brighter for all I know.

Running right through the Symposium were lectures and other contributions dealing directly with the methods and principles, physical and physicochemical, applicable to the determination of molecular structure, or to various examples of the use of such techniques in the solution of particular problems. Dr Thompson gave a general survey in his Symposium Lecture, and, though himself a pioneer of infra-red spectrometry, gave pride of place to X-ray crystallography, chiefly, I think, because that method gives full structural information, including a solution of the stereochemical problems. In passing, I would remark that structure determinations by classical methods should be followed by X-ray studies wherever possible. A good example is afforded by strychnine: after the long chemical trail had ended at the correct two-dimensional structure, the work of Bijvoet was still needed to determine the configuration of the molecule in space.

Dr Mathieson contributed an authoritative paper on the direct determination of molecular structure by physical methods alone, especially, of course, his own methods of X-ray crystallography. Indeed, Dr Mathieson has given several convincing demonstrations of the validity of the implied claim: one was the alkaloid cryptopleurine, an Australian natural product, but here I would like to make a few comments.

Dr Mathieson and other enthusiastic physicists and physical chemists are entirely justified in the exclusion of the organic chemist in order to prove

a point, namely, their contention that it is possible to determine molecular structure by physical methods alone.

Although this is true, it must not be supposed that the molecular structure is the be-all and end-all of the matter. It has been the objective of the classical organic chemist, who has approached molecular structure by the methods of analysis and synthesis which are familiar to all of us. But the great value of this work has been the approach—the analysis and the synthesis—and the region of chemistry which has been explored in that way. It has not been, perhaps, so much the final result. Even if we know the structure, we shall still have to explore the surrounding chemical territory. I shall give just a few examples. Would it have been a good thing for organic chemistry as a whole if the structure of indigo had been determined by just looking at a few milligrams of the pigment, so that Baeyer did not carry out the wonderful work which led, *inter alia*, to the determination of the structure? I think not. Another example is that of camphor since, even after the structure was known, there was a tremendous effort directed to the preparation of derivatives and study of the manifold molecular transformations which that Proteus among chemical substances undergoes. Thebaine is another case. Even when we knew the structure, we still had many difficult problems to tackle in order to reveal the full beauty of the wonderful complex of migratory processes that occur. Similarly for strychnine and cholesterol. Other examples will occur to you very easily. Thus it is not to be imagined that the knowledge of molecular structure is the end of the chapter. It is rather the chemistry which we encounter, in arriving at the molecular structure and in carrying out the synthesis, which is of the greater importance.

Many other applications of physical methods were brought to our notice. I would wish to refer particularly to the relatively new method of optical rotatory dispersion which was described so well by Professor Djerassi, and of which he is a pioneer and enthusiastic advocate. Many examples of the use of infra-red spectroscopy and of nuclear magnetic resonance occurred during the course of the Symposium, and these methods are undoubtedly among the most powerful tools which have been placed in our hands. The older method of ultra-violet spectroscopy is still an essential resource, and was found extremely useful by Professor Jones in his study of the acetylenic derivatives formed as products of the life processes of moulds. Throughout this Symposium, we have heard not only arguments in favour of physical methods, but also very good applications and justifications of this propaganda by the special determinations of structure which have been possible in that way.

One result of this gathering will have been a clarification of our ideas as to what each of the newer methods can actually do. Thus, optical rotatory dispersion gives stereochemical information which cannot be obtained from the ultra-violet or infra-red absorption spectra. The ultra-violet absorption is highly constitutive and, with increasing knowledge, what were thought to be vices turn out to be virtues; the electronic spectra show up the conjugative displacements and their changes under various conditions. Similarly, the extensive study of infra-red absorption has led to a better understanding of the scope of the constitutive effects in this region. The newer method of

VOL
2
1961

nuclear magnetic resonance is chiefly used to classify the hydrogen atoms in the molecule. It has proved a searching instrument, even in the case of complex alkaloids and the like.

The Symposium showed very great, and still growing, interest in the alicyclic polycyclic series, including the poly-iso-pentanoids. The brilliant lectures of Professor Barton and Professor Šorm require detailed attention for their appreciation; they certainly deserve close attention. The same applies to many other lectures and contributions, for example, those of Professor Brockman, and Professor Sørensen, in all of which important new results and correlations were disclosed.

We were greatly privileged to hear the lecture of Professor Woodward, in which he described, I believe for the first time, the outstanding achievement of the total synthesis of chlorophyll. Professor Woodward is not only a most brilliant *synthetic* organic chemist, who gives us metaphorical left hooks and right jabs in bewilderingly quick succession, but also an expositor able to convey a sense of the drama of the development to his audience. His lecture was thoroughly enjoyable, even thrilling, as an experience. No doubt in places he admitted to a little good fortune, though he also made it clear that it was expected. I was reminded of Benjamin Franklin's wise saying—" Luck is the bonus that accrues to industry ". Well, Woodward and his team were surely industrious. This achievement of the synthesis of chlorophyll is a very good example of the kind of comment that one often sees, " what good is it?" Presumably the " good thing ", as Woodward has so admirably pointed out himself, is the new knowledge that is obtained; increased understanding of the chemistry of chlorophyll, and of how it is likely to behave in a variety of circumstances. We do not know where that new knowledge may lead us, but it is certainly a most important substance and, therefore, we must know everything we can about it.

The Section Lecture of Dr Lederer was quite outstanding in interest and importance, and in promise for future developments. I had no means at hand for measuring the decibels of the applause, or its duration, but it was clear that my assessment was widely shared. Dr Lederer described extensive studies of biologically-active lipids produced by bacteria, especially the tubercle bacteria. Using every applicable modern technique he explained how several classical problems in the field have been finally solved, and, even more useful, he indicated the stages reached in the solution of others, including some that may have great significance for the therapy of tuberculosis in the future. I do not think that my high estimate of Professor Lederer's contribution is coloured too much by the fact that he agreed with some conclusions reached in our laboratory in Oxford, but certainly that gave me the near angle of sight which I mentioned previously, and I was able to appreciate the rest of it very much. Professor Lederer's modesty and humorous style charmed us, whilst the scientific matters adumbrated were positively exciting. His contribution to the Symposium will certainly be long remembered.

Several lectures and papers dealing with surveys of natural products were given, and Dr Price's talk on Australian natural product research showed how well the opportunities have been exploited here, largely under

the guidance of Dr Price himself. Incidentally, may I say that the visits to laboratories, for example those to the John Curtin Laboratory and to the C.S.I.R.O. Laboratories, were all very much appreciated. The closer contact with the work which we obtained in that way was extremely valuable.

It is very difficult to summarize the chemo-taxonomic work, of which a remarkable example is Professor Erdtman's study of the constituents of conifers. His genial approach and obvious enthusiasm for his subject were quite infectious, and I think that Erdtman has made an almost unique contribution to the application of organic chemistry to taxonomy. It is a good example that should be followed by other similar researches in that kind of direction.

I have not yet mentioned the alkaloids. Of course, there were many papers dealing with alkaloid chemistry, and I would like to mention particularly the lecture of Professor Stoll, which described the applications which natural product research might have in industry. These repercussions may indeed be important, but Stoll's work is just as academic (whatever that word means) as anyone else's. He has made extraordinarily valuable and unique contributions to the chemistry, for example, of the digitalis and ergot series.

VOL
2
1961

Another thread which has been running through the Congress was that of biogenesis, or relations of structures. Professor Birch, originally a Sydney student, and later a Professor here, gave many interesting further examples of the use of isotopic tracers in elaborating the hypothesis of the acetate condensations leading to natural products. But I think that the lecture of Dr Cornforth was another extremely important event in the Symposium—one of the real highlights.

The way in which Cornforth was able to describe the complete story of the synthesis of the iso-pentane skeleton, and then, for example, that of squalene, and through lanosterol to cholesterol and similar compounds, was quite remarkable. It was an extremely well prepared lecture, and of very great value to all of us. We admired the way in which the lecture was delivered, and found the matter, especially that which was contributed by Cornforth himself, quite fascinating. May I take this opportunity to say that Dr Cornforth was chiefly responsible for the successful termination of the first synthesis of the tetracyclic skeleton of the sterols which was effected in my laboratory at Oxford.

The scientific value of a symposium such as this is not wholly concentrated in the contributions. The opportunities it affords for personal contacts and discussions are also exceptionally valuable. That, I think, is part of the true raison d'être of a symposium such as this. It has been without question the most successful which I have ever followed. Never before has there been a symposium, concentrated on this section of organic chemistry, in which so many really significant papers have been delivered. Clear evidence of the enthusiasm of organic chemists in the last twenty years has been presented. The resurgence of interest has evidently been connected with the powers conferred by new techniques, which investigators have been as quick to adopt as the delays in delivery of apparatus permitted. We have had the great advantages conferred by new methods of separation including the ordinary methods of chromato-

graphy on paper or column, partition chromatography, vapour phase chromatography, and Craig separators. Naturally, the micro-methods, of analysis and manipulation, and the new physical methods of examination of the products have taken much of the tedium from our bench work and freed us for the harder tasks. The availability of isotopes has enormously stimulated interest in biogenesis because this can now be studied experimentally, instead of from the conjectural point of view; all these things have come together to produce a flood of research, of which we have had the clearest evidence in this Symposium. It has, therefore, been a most significant occasion, and we hope that it will be repeated, as is promised, in Czechoslovakia in 1962.

Finally, as there may not be another opportunity, may I say something not directly concerned with an estimate of the value of the Symposium? I want to refer to our President, Sir Alexander Todd. It would be presumptuous, again, for me, and impertinent, to discuss his Presidential Address: that is not, for my present purpose, a part of the symposium which I have attempted to cover. It was an inspiring review, and we all thoroughly enjoyed it. However, I do want to thank Sir Alexander Todd for acting as President of this Symposium, and also for the way in which he has assisted everybody in their various tasks. There is no question but that the success of this Symposium has been in large measure ensured by his Presidency.

VOL. 2 961

VOL.
2
1961

I.U.P.A.C. 1957 RULES FOR NOMENCLATURE OF ORGANIC CHEMISTRY ERRATA

The Commission on the Nomenclature of Organic Chemistry, at its meeting in Munich, 1959, authorized issue of the following errata to the 1957 Rules (Section A, Hydrocarbons; Section B, Heterocyclic Systems; also Steroids) (published by Butterworths Scientific Publications, London, 1958).

Page 9

A–2.3 (*iv*) Last formula:
Move the upper CH_3 to above the CH_2 attached to the carbon atom numbered 3.

A–2.3 (*v*) Last formula:
Add a double bond between carbon atoms numbered 1 and 2.

Page 15

A–3.6 Last formula:
Add a hydrogen to the carbon atom numbered 6.

Page 37

A–34.4 Change the name under the example to
10,11-Dihydro-5,10-*o*-benzeno-5*H*-benzo[*b*]fluorene.

Page 51

B–1.1, TABLE I
Change the valence for Tin and Lead from II to IV.

Page 54

B–2.11, item (7)
Change "isobenzofuranyl (3-shown)" to "isobenzofuranyl (1-shown)".

Note: The 3-form is the same as the 1-form. It would probably be clearer also to move the free valence to correspond to the 1-position of the parent compound.

Page 64

B–3.4(*c*) Correct the name under the example to
Imidazo[1,2-*b*][1,2,4]triazine.

Pages 74–82

For conformity with the practice in sections A and B of the rules, unsaturation indicated in names should conform with the conventions of *Chemical Abstracts*. This involves changes in the position of certain numerals. Names should then be altered as follows:

S–3.4, first two examples:
1,3,5(10)-Estratriene
1,3,5(10),6,8-Estrapentaene.

S–3.6, line 4:
20(22)-cardenolide.

S–3.7, line 5:
20,22-bufadienolide.
fourth example:
3*β*,14-Dihydroxy-4,20,22-bufatrienolide.

S–4.1, four examples:
11*α*,17,21-Trihydroxy-4-pregnene-3,20-dione.
6*β*-Hydroxy-4-pregnene-3,20-dione.
3,16*α*,17*α*-Trihydroxy-1,3,5(10)estratrien-11-one.
9-Chloro-17*β*-hydroxy-4-androsten-3-one.

S–6.1, second example:
18-Nor-4-pregnene-3,20-dione.

S–7.3, second example:
3-Hydroxy-D-dihomo-1,3,5(10)-estratrien-17b-one.

S–7.4, last two examples:
3-Hydroxy-16,17-seco-1,3,5(10)-estratriene-16,17-dioic acid.
9,10-Seco-5,7,10(19)-cholestatrien-3*β*-ol.

VOL. 2 1961